DISSERTATIONES SCHOLAE DOCTORALIS AD SANITATEM INVESTIGANDAM
UNIVERSITATIS HELSINKIENSIS

SEBASTIÁN PEÑA

SOCIOECONOMIC DIFFERENCES IN ALCOHOL USE, DISORDERS AND HARM: EXPLORING THE ALCOHOL HARM PARADOX

DEPARTMENT OF PUBLIC HEALTH SOLUTIONS
FINNISH INSTITUTE FOR HEALTH AND WELFARE AND
DEPARTMENT OF PUBLIC HEALTH
FACULTY OF MEDICINE
DOCTORAL PROGRAMME IN POPULATION HEALTH
UNIVERSITY OF HELSINKI

Department of Public Health
Faculty of Medicine
University of Helsinki

Department of Public Health Solutions
Finnish Institute for Health and Welfare

SOCIOECONOMIC DIFFERENCES IN ALCOHOL USE, DISORDERS, AND HARM

EXPLORING THE ALCOHOL HARM PARADOX

Sebastián Peña

ACADEMIC DISSERTATION

To be presented, with the permission of the Faculty of Medicine of the University of Helsinki, for public examination in Lecture Hall 1, Biomedicum, Haartmaninkatu 8, on January 22nd 2021, at 12 noon.

Helsinki 2021

Cover photo: Sergio Larraín, “On a boat from Puerto Aysén to Chiloé”, 1957

Dissertationes Scholae Doctoralis Ad Sanitatem Investigandam Universitatis Helsinkiensis 7/2021

ISBN 978-951-51-6919-8 (paperback)
ISBN 978-951-51-6920-4 (PDF)
ISSN 2342-3161 (print)
ISSN 2342-317X (online)

Printer Hansaprint
Helsinki 2021

The Faculty of Medicine uses the Urkund system (plagiarism recognition) to examine all doctoral dissertations

Supervised by

Research Professor Seppo Koskinen, MD, PhD
Department of Public Health Solutions
Finnish Institute for Health and Welfare
Helsinki, Finland

Research Professor Pia Mäkelä, PhD
Department of Public Health Solutions
Finnish Institute for Health and Welfare
Helsinki, Finland

Reviewed by

Adjunct Professor Leena Koivusilta, PhD
Department of Social Research
Faculty of Social Sciences
University of Turku
Turku, Finland

Associate Professor Antti Latvala, PhD
Institute of Criminology and Legal Policy
University of Helsinki
Helsinki, Finland

Opponent

Professor Alastair Leyland, PhD
MRC/CSO Social and Public Health Sciences Unit
University of Glasgow
Glasgow, United Kingdom

Abstract

Harmful alcohol use is a global public health challenge. Socioeconomic differences in alcohol-attributable harm are higher than in all-cause mortality and Finland has one of the highest socioeconomic differences in alcohol-attributable harm in European countries. Lower socioeconomic groups typically experience greater alcohol-attributable harm, despite reporting lower levels of alcohol use. This "alcohol harm paradox" can be the result of differential biases in the measurement of alcohol use, differential vulnerability to the effects of alcohol or reverse causality. What explains the alcohol harm paradox remains largely unknown.

This study investigated the existence and patterns of socioeconomic differences in volume of alcohol use and drinking patterns in Finland and Chile (two countries with high alcohol use and harm); examined changes in the prevalence and socioeconomic correlates of alcohol use disorders (AUD) in Finland between 2000 and 2011; and examined whether differential biases in the measurement of volume of alcohol use (using alcohol biomarkers as objective measures of alcohol use) and behavioural risk factors and their joint effects with each other and with socioeconomic status (SES) could explain the alcohol harm paradox.

We used data from national health surveys in Finland and also Chile in Sub-study I. The study population were adults residing permanently in Finland. Income and education were used as indicators of SES. Central measurements included alcohol use (volume and heavy episodic drinking), alcohol biomarkers (GGT, CDT, ALT and AST), smoking, body mass index as well as sociodemographic factors. We used structured interviews to assess 12-month and lifetime AUD and linked data from population surveys to mortality data. Outcomes were indicators of alcohol use, 12-month and lifetime prevalence of AUD and alcohol-attributable mortality. Statistical methods included the concentration index, logistic and Cox proportional hazards models and causal mediation analysis.

Abstinence was higher among lower socioeconomic groups than in higher socioeconomic groups in Finland and Chile, while heavy episodic drinking was modestly higher among people with lower SES in Finland. Estimated prevalence of 12-month AUD in Finland decreased from 4.6% in 2000 to 2.0% in 2011. We did not find evidence to support the existence of educational differences in AUD in 2000 or 2011. Participants in the lowest income quintile experienced 2.1 times higher risk of alcohol-attributable mortality, despite reporting lower levels of alcohol use. Alcohol biomarkers explained a very small fraction of the socioeconomic differences in alcohol-

attributable mortality. We found strong joint (or interactive) effects for SES and alcohol use and SES and smoking. However, smoking, body mass index and their joint effects with income explained a relatively small proportion (18%) of the effect of income on alcohol-attributable mortality.

Our results show inconsistent socioeconomic differences in alcohol use and AUD, but clearly higher risks of alcohol-attributable mortality in people of lower SES, confirming the alcohol harm paradox. Differential bias in the measurement of alcohol use and joint effects of behavioural risk factors explain a relatively small proportion of the alcohol harm paradox. Strong joint effects between SES and alcohol use suggest that differential vulnerability plays an important role in the alcohol harm paradox. Our findings support the need for targeted alcohol policies for lower socioeconomic groups and a broader policy agenda for tackling structural determinants of health.

Keywords: Socioeconomic status; Health inequalities; Alcohol use; Alcohol use disorders; Alcohol mortality; Smoking; Cohort studies; Concentration index; Multiple imputation; Measurement error; Causal mediation analysis.

Tiivistelmä

Alkoholin haitallinen käyttö on globaali haaste kansanterveydelle. Sosioekonomiset erot alkoholiin liittyvien haittojen jakautumisessa ovat suuremmat kuin kokonaiskuolleisuudessa, ja alkoholiin lliityvien haittojen sosioekonomiset erot ovat Suomessa suuremmat kuin useimmissamuissa Euroopan maissa. Alemmissa sosioekonomisissa ryhmissä alkoholiin liittyviä haittoja esiintyy enemmän huolimatta siitä, että alkoholin käyttö on vähäisempää. Tämä alkoholihaittojen paradoksi voi johtua vääristymistä alkoholin käytön mittauksessa, erilaisesta herkkyydestä alkoholin aiheuttamille haitoille tai käänteisestä syy-yhteydestä. Alkoholihaittojen paradoksin syy on edelleen melko tuntematon.

Tässä tutkimuksessa selvitettiin alkoholin käytön sosioekonomisten erojen olemassaoloa ja malleja Suomessa ja Chilessä (: joissa kummassakin alkoholia käytetään runsaasti ja siitä aiheutuu paljon haittoja); tarkasteltiin alkoholihäiriöiden (alkoholiriippuvuus ja alkoholin haitallinen käyttö) yleisyyden ja sosioekonomisten erojen muutoksia Suomessa vuosina 2000–2011; ja tutkittiin, selittävätkö virheet alkoholin käytön mittaamisessa (käyttäen biomarkkereita objektiivisina alkoholin käytön mittareina) ja käyttäytymiseen liittyvät riskitekijät ja niiden yhteisvaikutukset alkoholihaittojen paradoksin.

Käytimme tutkimusaineistona kansallisia terveystutkimuksia Suomesta ja osatutkimuksessa I Chilestä. Suomalaisissa aineistoissa tutkittavat olivat maassa pysyvästi asuvia aikuisia. Sosioekonomista asemaa kuvattiin tulojen ja koulutuksen avulla. Keskeisiä muuttujia olivat alkoholinkäyttö, alkoholiin liittyvät biomarkkerit (GT, CDT, ALAT ja ASAT), tupakointi, painoindeksi sekä sosiodemografiset muuttujat. Käytimme strukturoituja haastatteluja edeltäneen vuoden ja eliniän aikana esiintyneen alkoholihäiriön toteamiseen. Väestötutkimusten tiedot yhdistettiin kuolleisuustietoihin. Päätemuuttujia olivat alkoholin käyttöä mittaavat muuttujat, alkoholihäiriön esiintyvyys 12 viime kuukauden ja eliniän aikana sekä alkoholikuolleisuus. Tilastollisina menetelminä käytettiin konsentraatioindeksiä, logistista ja suhteellisten riskitiheyksien (Coxin) mallia, ja syy-seuraussuhteen mediaatioanalyysia.

Raittius oli tavallisempaa alemmissa kuin ylemmissä sosioekonomisissa ryhmissä Suomessa ja Chilessä, mutta myös humalajuominen oli hieman yleisempää näissä ryhmissä. 12 kuukauden alkoholihäiriön esiintyvyys laski 4,6 prosentista vuonna 2000 2,0 %:iin vuonna 2011. Emme havainneet sosioekonomisia eroja alkoholihäiriöiden esiintyvyydessä vuosina 2000 tai 2011. Alkoholikäyttöön liittyvät biomarkkerit selittivät hyvin pienen osan sosioekonomisista

eroista alkoholikuolleisuudessa. Sosioekonomisen aseman ja alkoholinkäytön sekä sosioekonomisen aseman ja tupakoinnin välillä oli vahvoja yhteisvaikutuksia. Tupakointi, painoindeksi ja niiden yhteisvaikutukset selittivät kuitenkin suhteellisen pienen osan (18%) tulojen vaikutuksesta alkoholikuolleisuuteen.

Tutkimuksessa todettiin vaihtelevia sosioekonomisia eroja alkoholin käytössä ja alkoholihäiriöiden esiintyvyydessä, mutta selvästi korkeampi alkoholikuolleisuus matalammissa sosioekonomisissa ryhmissä, mikä vahvistaa alkoholihaittojen paradoksin olemassaolon. Alkoholinkäytön mittaamisessa esiintyvät poikkeamat ja terveyskäyttäytymisen riskitekijöiden yhteisvaikutukset selittivät suhteellisen pienen osan alkoholin haittojen paradoksista. Sosioekonomisen aseman ja alkoholinkäytön vahvat yhteisvaikutukset viittaavat siihen, että erilaisella haavoittuvuudella on tärkeä rooli alkoholihaittojen paradoksissa. Tuloksemme : korostavat tarvetta kehittää alempiin sosioekonomisiin ryhmiin kohdennettua alkoholipolitiikkaa ja terveyden rakenteellisten tekijöiden huomioimista poliittisessa päätöksenteossa.

Asiasanat: Sosioekonominen asema; Terveyserot; Alkoholin käyttö; Alkoholihäiriöt; Alkoholikuolleisuus; Tupakointi; Kohorttitutkimukset; Konsentraatioindeksi; Moni-imputointi; Syy-seuraussuhteen mediaatioanalyysi.

Resumen

El consumo nocivo de alcohol es un problema global de salud pública. Las diferencias socioeconómicas en daño atribuible al alcohol son mayores que aquellas en mortalidad general y Finlandia tiene una de las diferencias socioeconómicas en daños atribuible al alcohol más altas de Europa. El nivel socioeconómico (NSE) bajo se asocia a mayor daño atribuible al alcohol, a pesar de reportar menores niveles de consumo de alcohol. Esta "paradoja del daño por alcohol" puede ser el resultado de sesgos diferenciales en la medición del consumo de alcohol, vulnerabilidad diferencial a los efectos del alcohol o causalidad reversa. Qué explica esta paradoja se desconoce en gran medida.

El propósito del estudio fue investigar la existencia y patrones de desigualdades socioeconómicas en el consumo de alcohol en Finlandia y Chile (dos países con alto consumo y daño por alcohol); evaluar cambios en la prevalencia y correlaciones socioeconómicas en el trastorno por consumo de alcohol (TCA) en Finlandia entre el año 2000 y 2011; y evaluar si los sesgos diferenciales en la medición del consumo de alcohol (utilizando biomarcadores de alcohol como indicadores objetivos del consumo) y los factores de riesgo conductuales y sus efectos conjuntos pueden explicar la paradoja del daño por alcohol.

Se utilizaron datos de encuestas nacionales de salud de Finlandia (también Chile en el Sub-estudio I). La población estudiada fueron adultos que residían de forma permanente en Finlandia. Se utilizaron el ingreso del hogar y la educación como indicadores de NSE. Otras mediciones incluyeron el consumo de alcohol (volumen y consumo episódico excesivo) biomarcadores de alcohol (GGT, CDT, ALT y AST), tabaquismo, índice de masa corporal e indicadores sociodemográficos. Se utilizaron entrevistas estructuradas para evaluar la prevalencia de TCA en 12 meses y durante toda la vida y se vincularon los datos de encuestas poblacionales con datos de mortalidad. Los outcomes variaron, incluyendo indicadores de consumo de alcohol, prevalencia de 12 meses y durante la vida de TCA y mortalidad atribuible al alcohol. Se utilizaron diversos métodos estadísticos como el índice de concentración, modelos de regresión logística y de riesgos proporcionales de Cox y análisis de mediación causal.

La prevalencia de abstinencia fue mayor en participantes de NSE bajo en Finlandia y Chile, mientras que el consumo episódico excesivo fue ligeramente mayor en personas de NSE bajo en Finlandia. La prevalencia estimada de TCA de 12 meses disminuyó de 4.6% en el año 2000 a 2.0% en el año 2011. No encontramos evidencia que apoyara la existencia de desigualdades

socioeconómicas en la prevalencia de TCA en el año 2000 ni el 2011. Los biomarcadores de alcohol explicaron una muy pequeña fracción de las diferencias socioeconómicas en mortalidad atribuible al alcohol. Se encontraron claros efectos combinados (interactivos) para NSE y consumo de alcohol y NSE y tabaquismo. Sin embargo, el tabaquismo e índice de masa corporal y sus efectos conjuntos con ingreso explicaron sólo el 18% del efecto del ingreso en la mortalidad atribuible al alcohol.

Los resultados del estudio sugieren diferencias inconsistentes en el consumo de alcohol y TCA, pero claros mayores riesgos de mortalidad atribuible al alcohol en personas de NSE bajo, confirmando la paradoja del daño por alcohol. Sesgos diferenciales en la medición del alcohol y efectos conjuntos de factores de riesgo conductuales explicaron una proporción relativamente pequeña de la paradoja del daño por alcohol. Los claros efectos combinados entre NSE y alcohol sugieren que la vulnerabilidad diferencial juega un rol importante en la paradoja por daño de alcohol. Estos hallazgos apoyan la necesidad de políticas de alcohol focalizadas en niveles socioeconómicos bajos y una agenda política amplia para abordar los determinantes estructurales de la salud.

Keywords: Nivel socioeconómico; Desigualdades en Salud; Consumo de Alcohol; Trastorno por Uso de Alcohol; Mortalidad por alcohol; Tabaquismo; Estudios de cohorte; Índice de concentración; Imputación múltiple; Error de medición; Análisis de mediación causal.

Acknowledgements

This study was conducted between 2012 and 2020 at the Finnish Institute for Health and Welfare. I am grateful to the former heads of the Department of Population Health, Functional Capacity and Wellbeing and the current head of the Public Health Evaluation and Projection Unit, Dr Jukka Jokinen for providing excellent research facilities and a supportive work environment. I wish to thank Professor Hannu Sariola, Director of the Doctoral School in Health Sciences, and Professor Samuli Ripatti, Director of the Doctoral Programme in Population Health, for the opportunity to study in the graduate school and the financial support between 2018 and 2020. In addition to the Doctoral Programme in Population Health, this study was financially supported by the Finnish Medical Foundation, the Finnish Foundation for Alcohol Studies and the Juho Vainio Foundation. I am very grateful for all the funding received.

I owe my deepest gratitude to my supervisors, Research Professor Seppo Koskinen and Research Professor Pia Mäkelä. I am eternally grateful to Seppo for taking a leap of faith with me to be part of the planning of the Health 2011 Survey. This was my first job in public health and set the standards on how kindness and collaboration should be at the centre of any research work. His advice has always been friendly, constructive and thought-provoking, and has pushed me to think broadly on the societal importance of my research work.

I am deeply grateful to Pia, who has always been there for me. I greatly appreciate her positive, constructive and pragmatic feedback. Her capacity to ask difficult questions has challenged me to transmit my ideas with greater clarity and precision and has helped me to clear my mind at times things were blurry. I admire her balanced combination of strong conceptual understanding and analytical skills.

I am grateful to the reviewers of this thesis, Adjunct Professor Leena Koivusilta and Associate Professor Antti Latvala, for their thorough and constructive suggestions, which helped to make this summary more coherent and clearer.

My warm thanks to the thesis committee Professor Ossi Rahkonen, Professor Pekka Martikainen and Adjunct Professor Tomi Lintonen for their encouragement and advice.

I am deeply honoured to have worked with great co-authors, who generously shared their expertise and provided insightful suggestions to improve the manuscripts. Thank you, Gonzalo Valdivia, Satu Helakorpi, Niina Markkula, Paula Margozzini, Jaana Suvisaari, Tommi Härkänen, Suoma Saarni, Janne Härkönen, Markku Heliövaara, Teemu Gunnar, Satu Männistö,

Tiina Laatikainen and Erkki Vartiainen. Special thanks to Tommi Härkänen for his support in the design and implementation of statistical methods and his incredible responsiveness when I've been stuck in a complex methodological challenge. I am also thankful to Anne Juolevi, Harri Rissanen and Tuija Jääskelainen for their deep knowledge of the datasets I've worked with and their support in obtaining the data, and to Jonas Sundman and Tuomo Nieminen for their help to access the Biometry Linux Cluster and infinite patience with my memory-intensive analyses that sucked processing power for weeks. To all my colleagues at the Public Health Evaluation and Projection Unit and the Mental Health Unit, thank you for letting me be part of such nice and collaborative work environment.

I am grateful to have worked with great colleagues in Chile and different parts of the world. Thank you Cristóbal, Pedro, Francisca, Alfredo, Pablo, Álvaro, Marcela, Camila, Sofía, Cecilia, Jaime, José Ignacio, Maja, Macarena, Helena, Karen, and other colleagues in PoliMap, for your enthusiasm and perseverance in pushing those projects together. I am thankful to my colleagues in the Municipality of Santiago and my team in Santiago Sano, who were always enthusiastic and supportive of my wildest ideas. I am thankful to the #epitwitter community and all those anonymous researchers who helped me through difficult methodological questions and provided inspiration at times where my motivation was running low.

To my friends Andrés, William, Julio, Juan Luis, José Luis, Cristian, Jorge, María Jesús, Marcela, Paula, Blas, Andrés, thank you for your friendship and support all those years. Thank you, Seppo, Tommi, Jari, Tero, Ossi, Juha, Ari, Olli, Saju, Kuu, Jonne, for introducing me to badminton and enduring my slow learning and blasphemies in Spanish over the years. Special thanks to Paula, Pauli, Daniel and Iván for your support in these recent difficult times.

Finally, my deepest gratitude to my family. To my parents, for their unconditional support and for teaching me a sense of duty and commitment for a better world. To Pauli, for being such a great sister and person, enduring my older-brother-bullying and always been there for me. To Karime, Karime and Nayi, for your constant love and understanding. To Ritva, Pekka and Emppu, for all the support, love and moose meat one can hope for. To my children, Sebastián, Alvar and Violeta, for the blessing of being your father and your help in keeping me grounded to what is truly important. Special thanks to Niina, my companion for most of this trip. Thank you for listening to me, for your honest and pragmatic advice, for your love.

Helsinki, December 2020
Sebastián Peña

Table of contents

List of Original Publications

This thesis is based on the following publications:

I Peña S, Mäkelä P, Valdivia G, Helakorpi S, Markkula N, Margozzini P and Koskinen S. Socioeconomic inequalities in alcohol consumption in Chile and Finland. Drug Alcohol Depend 2017; 173: 24-30.

II Peña S, Suvisaari J, Härkänen T, Markkula N, Saarni S, Härkönen J, Mäkelä P and Koskinen S. Changes in prevalence and correlates of alcohol-use disorders in Finland in an 11-year follow-up. Nord J Psychiatry 2018; 72: 512-520.

III Peña S, Mäkelä P, Härkänen T, Heliövaara M, Gunnar T, Männistö S, Laatikainen T, Vartiainen E, Koskinen S. Measurement error as an explanation for the alcohol harm paradox: analysis of eight cohort studies. Int J Epidemiol 2020. In press https://doi.org/10.1093/ije/dyaa113

IV Peña S, Mäkelä P, Härkänen T, Heliövaara M, Männistö S, Laatikainen T, Koskinen S. Joint effects of alcohol use, smoking and body mass index as an explanation of the alcohol harm paradox: causal mediation analysis of eight cohort studies. Resubmitted.

The publications are referred to in the text by their roman numerals. Original publications are reprinted with kind permission of the copyright holders.

Abbreviations

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUD	Alcohol use disorders
AVTK	Health Behaviour and Health among the Finnish Adult Population
CIDI	Composite International Diagnostic Interview
CDT	Carbohydrate -deficient transferrin
DALYs	Disability-adjusted life years
DSM	Diagnostic and Statistical Manual of Mental Disorders
e.g.	*exempli gratia*
FINRISK	National FINRISK Study
GGT	Gamma glutamyl-transferase
H2000	Health 2000 Survey
H2011	Health 2011 Survey
HED	Heavy episodic drinking
HICs	High-income countries
HR	Hazard ratio
ICD	International Classification of Diseases
i.e.	*id est*
LMICs	Low- and middle-income countries
MFS	Mini-Finland Survey 1978-1980
MSM	Marginal Structural Model
NCDs	Non-communicable diseases
OR	Odds ratio
OECD	Organization for Economic Co-operation and Development
PAF	Population attributable fraction
RR	Rate ratio
RRR	Ratio of relative risk
SES	Socioeconomic status
WHO	World Health Organization

1 Introduction

Harmful alcohol use is a major risk factor of death and disability. Globally, alcohol use is associated with almost 3 million deaths and was the seventh risk factor for both death and DALYs (a composite measure of death and disability) in 2016. It was the leading risk factor for death among 15 to 49 years old (GBD 2016 Alcohol Collaborators, 2018).

Alcohol use has negative health, social and economic impacts, which tend to disproportionately fall on lower socioeconomic groups. According to a meta-analysis, low educated men and women experience 2.9 and 2.7 times higher alcohol-attributable mortality than their counterparts with high education (Probst, et al., 2015). Similar socioeconomic differences have been described for alcohol-attributable hospitalizations (Sadler, et al., 2017). These socioeconomic differences in alcohol-attributable harm are important *per se* as they are considered unfair and unjust, but also because they are an important contributor to overall socioeconomic inequalities in health. In Finland, socioeconomic differences in alcohol-attributable mortality are relatively high compared to other European countries (Mackenbach, et al., 2015). In 2007, alcohol-related deaths represented 43% and 23% of all deaths in Finnish working-aged men and women in the lowest income quintile (Tarkiainen, et al., 2016).

Despite experiencing greater alcohol-attributable harm, lower socioeconomic groups report lower or similar alcohol use, a discrepancy known as the alcohol harm paradox (Bellis, et al., 2016). Three factors can explain the paradox: (i) differential bias in the measurement of alcohol use, where harmful drinking among lower socioeconomic groups is not captured by self-reported instruments; (ii) differential vulnerability to risk factors, where lower socioeconomic groups experience disproportionately greater alcohol-attributable harm due to joint effects between alcohol use and risk factors; and (iii) reverse causality, where harmful drinkers experience a reduction in their socioeconomic status. What explains the alcohol harm paradox remains largely unknown.

In this study, we advance the field by exploring potential pathways and explanations for the alcohol harm paradox. We begin by exploring whether the inconsistent findings on socioeconomic differences in alcohol use could be addressed by using a novel methodological approach (i.e. a summative measure called the concentration index) and several indicators of

alcohol use. We continue by examining the existence of socioeconomic differences in alcohol use disorders and the change in their prevalence. Finally, we assess two possible explanations of the alcohol harm paradox: (i) differential bias in the measurement of exposure, or whether using an objective measure of alcohol use (i.e. alcohol biomarkers) could address the explanation that measurement error in alcohol use explains the paradox, and (ii) behavioural risk factors and their joint effects with each other and with SES, considering that lower socioeconomic groups tend to smoke more and have higher body mass index and there could be joint effects with alcohol use, leading to increased mortality.

For this purpose, we used data from national population health surveys in Finland (and Chile in Sub-study I), which is a highly developed country with high alcohol consumption and alcohol-attributable harm.

The rest of this book continues as follows: Section 2 includes a literature review of the socioeconomic differences in alcohol use, alcohol use disorders and harm, as well as the potential explanations for the alcohol harm paradox provided in the current literature and the empirical evidence supporting them. Section 3 describes the aims of the study. Section 4 explains the settings, design, participants, data sources and methods used in the study. Section 5 describes the results of the study. Section 6 provides a discussion of the findings and threats to validity and provides public health implications. Section 7 concludes and describes ideas for future research.

2 Review of the literature

2.1 ALCOHOL USE

2.1.1 DEFINITIONS AND EPIDEMIOLOGY

Alcohol (ethanol) is a psychoactive substance produced by fermentation of sugar-rich substrates, such as fruits, grains, starchy plants and other sources of sugar (Ciani, et al., 2008). Alcohol has been consumed since ancient times (the earliest evidence is from China 7,000 years B.C.) as a food, medicine, recreational substance, social facilitator and religious symbol (Keller, 1979, McGovern, et al., 2004).

There are three main types of alcoholic beverages: beer (and ciders), wine and spirits. In Europe, the local availability of malting barley and grapes resulted in the predominant consumption of beer (usually of low alcoholic content) and wine, until the advent of the distillation process in the 1500s (Keller, 1979). This led to the emergence of distilled liquors, such as gin, vodka or whiskey, which became the predominant alcoholic beverage in countries like Finland, Sweden, Norway and the United Kingdom (Blocker, et al., 2003). Home distillation was relatively common until the mid-1800s, when tighter licensing regulations and excise taxes came into force (Blocker, et al., 2003). During the Industrial Revolution, large industrial breweries were created in most countries, resulting in the massive production of beer of usually higher alcohol content (Blocker, et al., 2003). Regional differences in alcohol use in Europe started to erode since the 1960s, especially in countries where beer and spirits were the predominant alcoholic beverage, and the share between beer, wine and spirits have started to equalize in Europe and worldwide (Holmes and Anderson, 2017).

From a public health perspective, the most crucial dimensions of alcohol use are the volume of alcohol consumed and the drinking patterns. In other words, how much alcohol is consumed and how. Globally, most of the population aged 15 and over are either lifetime abstainers or former drinkers. However, drinkers exceed non-drinkers in three WHO regions: the European Region (59.9% are current drinkers), the Americas (54.1%) and the Western Pacific Region (53.8%) (World Health Organization, 2018).

In 2016, the annual total alcohol per capita consumption in the population aged 15 years and over was 6.4 litres of pure alcohol worldwide, which translates into 13.9 grams of pure alcohol per day (a bit more than 1 can of beer per day). In the European region, average consumption in 2016 was 9.8 litres of pure alcohol per capita per year, equivalent to 21.3 grams of pure alcohol per capita per day (World Health Organization, 2018). While total alcohol consumption in the world has increased since 2000, total alcohol consumption has decreased in the European Region as a whole and in almost three fourths of the European countries (World Health Organization, 2018).

Drinking patterns resemble the total alcohol consumption. Prevalence of heavy episodic drinking among those aged 15+ years (HED, defined as the use of 60 or more grams of pure alcohol on a single occasion at least once per month) in 2016 was the highest in the European Region (26.4%), the Western Pacific Region (21.9%) and the Americas (21.3%). The prevalence of HED has declined worldwide (World Health Organization, 2018).

2.1.2 MEASUREMENT OF ALCOHOL USE

Alcohol use can be measured either at the population level (such as the total alcohol consumption estimates provided above) or at the individual level. At the population level, total alcohol per capita consumption is considered the most valid indicator of alcohol use, as it derives mostly from reliable sources such as excise duties, sales, import and export statistics (Henderson, et al., 2016, Rehm and Scafato, 2011, Sordo, et al., 2016).

At the individual level, the measurement of alcohol use aims to capture several distinctive dimensions: first, drinking status, to distinguish never, former and current drinkers; second, the volume of alcohol consumed; third, drinking patterns, including drinking frequency (how often), drinking occasions (at which time of the day, with or without meals), the drinking environment (where) and the type of beverage consumed; and fourth, drinking trajectories, including the within-individual variability between days, weeks and periods of the year as well as the long-term trajectories (Gmel and Rehm, 2004).

Self-reports are the dominant approach to measuring alcohol use, as they allow us to examine drinking patterns and the distribution of consumption in population groups. Individuals might be asked about their previous alcohol use (retrospective assessment) or to register their use over a period of time (prospective assessment) (Keogh, et al., 2012). Detailed retrospective assessments, such as the Timeline Follow Back and extensive instruments in

drinking surveys, are able to provide a more accurate picture of the volume, patterns and trajectories of alcohol use (Casswell, et al., 2002, Sobell and Sobell, 1992). Real-time assessment is also possible with methods such as the Ecological Momentary Assessment (Wray, et al., 2014).

General population health surveys usually enquire about a wide range of population health risk factors and dedicate less time for the assessment of alcohol use. Alcohol instruments in general health surveys often assess the quantity and frequency of alcohol use, either in general or using beverage-specific questionnaires (quantity-frequency or graduated quantity-frequency, QF or GQF). Drinking patterns are usually captured by questions on the frequency of exceeding a predefined number of drinks in a single occasion. Time window for the assessment varies from an unspecified "typical" time period to the last year, month, week or day (Gmel and Rehm, 2004).

Population health surveys normally capture 40-50% of the alcohol use estimates derived from alcohol sales (Livingston and Callinan, 2015). This suggests that the total amount of alcohol use is underreported in surveys. In the next sections, two sources of undercoverage are briefly discussed: selection bias and measurement error.

2.1.3 SELECTION BIAS

Population health surveys collect data from participants who consent to participate in the study. However, participants and non-participants might not have the same characteristics, resulting in systematic differences between the participants studied and the population of interest (Henderson and Page, 2007). Selection bias in population health surveys can arise from two phenomena (which can coexist). First, individuals with high alcohol use (and risk of alcohol-attributable harm) are not eligible to participate in the survey. This is called sampling frame bias and derives from imperfect sampling frames (McCutcheon, 2008). Most commonly, individual-based sampling frames contain missing elements, excluding certain population groups such as homeless, those living in institutions, conscripts or temporary migrants (e.g. migrant workers or refugees). Some of these population groups can have a higher prevalence of heavy drinkers or people who drink in unhealthier patterns (Mäkelä and Huhtanen, 2010).

A second important selection bias comes from non-participation. Studies have consistently shown that non-respondents are more often younger, male, of low socioeconomic status and divorced or widowed (Harald, et al., 2007, Knudsen, et al., 2010, Maclennan, et al., 2012,

Reinikainen, et al., 2018, Tolonen, et al., 2006, Tolonen, et al., 2019). These population groups can also have a higher prevalence of heavy volume drinkers or heavy episodic drinkers.

2.1.4 MEASUREMENT ERROR

Another challenge is the measurement of alcohol use. First, population surveys need to capture adequately the within-person variability. Consider the four hypothetical drinkers depicted in Figure 1. Over a 1-year period, drinker A consumed alcohol in low amounts on a few occasions. Drinker B consumed larger amounts of alcohol concentrated on a few days per year. Drinker C drank constantly one drink per day. Drinker D drank on most days and in larger amounts (often exceeding 60 grams) mostly over weekends. Using a 7-day window, drinkers A and B could be misclassified as a non-drinker. Drinker C might be inaccurately considered a heavy drinker. Using a 12-month reference period, questions about frequency and typical quantity might not reveal the heavy episodic drinking of drinker D and might yield similar estimates of the volume consumption among drinkers C and D.

A second source of measurement error is information bias. Participants might fail to remember accurately their consumption (recall or memory bias), especially with longer recall periods (Ekholm, 2004) or might adjust their responses to what they consider to be socially expected (social desirability bias). Participants might be given restricted categories as possible answers and the upper level category might underestimate the true value of consumption (truncation or top-coding bias) (Fichtenbaum and Shahidi, 1988).

These two sources of measurement error could potentially bias our estimates of alcohol use, resulting in an absolute underestimation of the total alcohol used, as well as a relative underestimation if these biases operate differentially by population groups. There is substantive evidence of systematic absolute underestimation when comparing survey estimates with alcohol sales or other more valid proxies of population level alcohol use (Henderson, et al., 2016, Robinson, et al., 2013, Stockwell, et al., 2004).

A primary concern in this study is the potential relative underestimation by socioeconomic groups (Boniface and Shelton, 2013, Devaux and Sassi, 2016). This means that the biases described above are not uniform across social groups. For example, lower socioeconomic groups could have different perceptions on the stigma of heavy alcohol use and be less inclined to report their drinking accurately. An equal underreporting biases absolute estimates (in the case of alcohol use, downwards), but does not distort the associations between socioeconomic groups.

Figure 1. Drinking trajectories over a 1-year period in four hypothetical drinkers

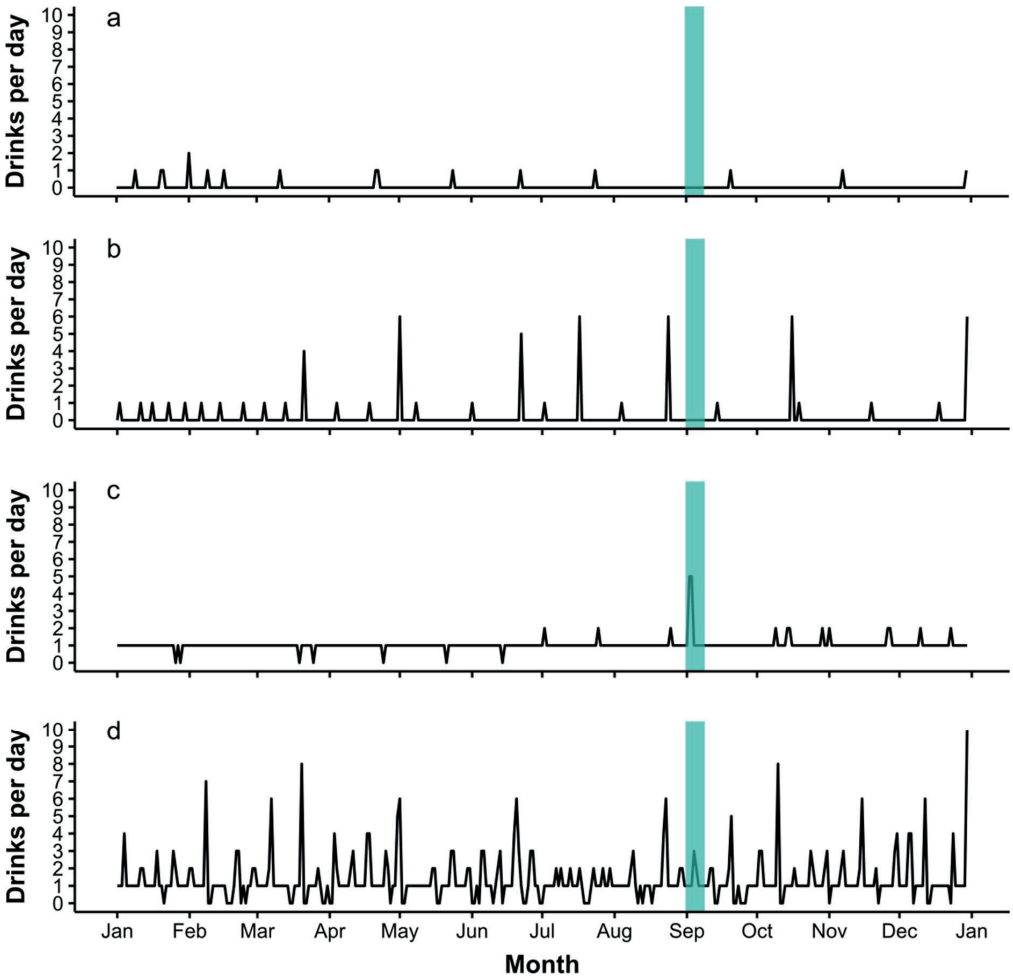


Figure 1a represents a drinker of low amounts on a few occasions. Figure 1b represents a drinker of larger amounts of alcohol concentrated in a few days per year. Figure 1c represents a drinker who constantly drinks one drink per day. Figure 1d represents a drinker who drank on most days and in larger amounts (often exceeding 60 grams) mostly over weekends. The shaded area represents a 7-day study window

Only one study in 13 OECD countries has indirectly explored this relative underestimation. The authors examined the impact of correcting for self-report bias on the measurement of socioeconomic inequalities in alcohol use. Survey-based alcohol use was corrected to reflect the overall total per capita consumption in each country, assuming a latent gamma distribution to correct the volume of alcohol use upwards. After correcting for self-report bias, hazardous drinking rates increased among those with higher education and decreased among those with lower education in both men and women (Devaux and Sassi, 2016).

2.1.5 ALCOHOL BIOMARKERS

Alcohol biomarkers are a potential tool to account for measurement error, since these are objective measures of alcohol use and not subject to information bias. It is possible to measure ethanol and its metabolites directly (direct biomarkers) or indirectly using markers of their toxic effects on organs, tissues or body biochemistry (Ingall, 2012).

Direct alcohol biomarkers measure ethanol and its metabolites using samples from sources such as blood, breath, urine, hair and skin. Ethanol has a short half-life and is a measure of alcohol use during the past hours. Alcohol metabolites, such as ethyl glucuronide (EtG), ethyl sulfate (EtS) and phosphatidylethanol (PEth) can be measured until up to four weeks of alcohol use. These direct biomarkers have mostly been used in medico-legal (drink driving, prisons), forensic and clinical settings. Recently, the use of monitors that continuously measure alcohol vapours through perspiration has emerged as a promising tool whose use in population health surveys remains to be tested (Greenfield, et al., 2014).

Indirect biomarkers are often used in population health surveys, since they provide information over longer time periods than direct alcohol biomarkers. The most commonly used indirect biomarkers are gamma-glutamyltransferase (GGT), carbohydrate-deficient transferrin (CDT), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) (Table 1).

GGT is a glycoenzyme found in endothelial cell membranes in the liver, spleen, kidney, pancreas and biliary tree. Serum GGT comes exclusively from the liver. The function of GGT is to protect cells from oxidative stress during metabolism by keeping high intracellular levels of glutathione (an intracellular antioxidant) (van Beek, et al., 2014, Whitfield, 2001). GGT is an indicator of heavy alcohol intake and a marker of oxidative stress (Litten, et al., 2010, Niemelä, 2016). Sensitivity varies between 34-85% and specificity varies between 11-85% depending on the population and measures of alcohol use (Montalto and Bean, 2003). The role of GGT is not specific to prevent alcohol-induced oxidative stress, and GGT activity has also be shown to increase with smoking (Wannamethee and Shaper, 2010) and obesity, as well as with diabetes, hypertension, cardiovascular disease, metabolic syndrome, stroke and COPD (Alatalo, et al., 2008, Du, et al., 2013, Kunutsor, et al., 2015, Lee, et al., 2001).

CDT are forms of transferrin with a lower number of sialic acid chains. Transferrin, a polypeptide involved in iron metabolism, structurally consists of two N-linked polysaccharide chains, branched by sialic acid residues. Depending on the level of sialylation, there are isoforms of transferrin with zero, one, two, three, four or five sialic acid chains (Solomons, 2012).

Table 1. Direct and indirect alcohol biomarkers

Biomarker	Description	Time frame
Direct biomarkers		
Ethyl glucuronide (EtG)	Nonoxidative metabolite of alcohol. Detectable on blood, urine and saliva.	Detectable in urine for 2 to 5 days after alcohol cessation in heavy drinkers.
Ethyl sulfate (EtS)	Nonoxidative metabolite of ethanol. Detectable on blood, urine and saliva.	Detectable in urine for 2 to 5 days after alcohol cessation in heavy drinkers.
Fatty acids ethyl esters (FAEEs)	Nonoxidative products of ethanol metabolism. Detectable in blood, hair and meconium.	Detectable in blood for days after alcohol cessation and for several months in hair and meconium.
Phosphatidylethanol (PEth)	Ethanol metabolite produced as a result of the combination of alcohol and fatty acids.	Detectable for up to 4 weeks after alcohol cessation.
Indirect biomarkers		
Gamma-glutamyltransferase (GGT)	Hepatic microsomal enzyme. Serum GGT increases due to release from the cell membrane (e.g. with repeated alcohol use) and damage of liver cells (e.g. by alcohol, hepatotoxic drugs, ischemia and viral hepatitis). GGT levels also increase by nonalcoholic liver diseases, hepatobiliary disorders, obesity, diabetes and smoking, limiting the specificity.	Returns to normal in 2-3 weeks after alcohol cessation.
Carbohydrate-deficient transferrin (CDT)	Glycoprotein synthesized in the liver. Heavy alcohol use increases the fractions of isoforms deficient in sialic acid.	Returns to normal in 2-5 weeks after alcohol cessation.
Alanine aminotransferase (ALT)	Enzyme found primarily in liver and skeletal tissue.	High levels reflect liver dysfunction in alcohol users.
Aspartate aminotransferase (AST)	Hepatocellular enzyme, also present in heart, muscle, kidney, brain, pancreas, lung, leukocytes and erythrocytes.	High levels reflect liver dysfunction in alcohol users.
Mean corpuscular volume (MCV)	Measure of red blood cell size. Average MCV is elevated in heavy drinkers, but also in vitamin B12 or folate deficiency, hypothyroidism, haemolytic anaemia.	Returns to normal in 2-4 weeks after alcohol cessation.

Source: Conigrave, et al., 2003, Ingall, 2012, Niemelä, 2016

Ethanol directly inhibits the enzymes responsible for the addition of sialic acid chains and induces sialidase that removes sialic acid chains (Bomford and Sherwood, 2014).

CDT is, therefore, a highly specific marker of sustained heavy alcohol use, reversing after 14-21 days of abstinence. CDT is a more specific and sensitive measure of chronic alcohol use than GGT, with sensitivity and specificity varying between 44-94% and 82-100% respectively (Montalto and Bean, 2003).

ALT and AST are enzymes that catalyse the conversion of amino acids and oxoacids by transfer of amino groups (Vroon and Israili, 1990). ALT is located only in the cytoplasm and is highly active in the liver and in lower levels in the kidney, heart and muscle (Botros and Sikaris, 2013, Tavakoli, et al., 2011). AST is present in both the cytoplasm and mitochondria and has the highest activity in the heart, liver, kidney and muscle. In healthy individuals, both ALT and AST circulate in the blood due to hepatocyte turnover and cytoplasmic budding or bleeding (Botros and Sikaris, 2013). Elevated ALT and AST levels are indicative of cellular damage, but elevations over 10 times the reference level are indicative of hepatic cell injury (Giannini, et al., 2005). ALT is more specific for liver conditions than AST and a ratio of AST:ALT greater than 2:1 supports alcohol as an etiological factor (Niemelä and Alatalo, 2010). ALT has a sensitivity of 32-50% and a specificity of 87-92% in detecting heavy alcohol use. AST has a sensitivity of 47-68% and a specificity of 80-95% in detecting heavy alcohol use. (Torruellas, et al., 2014).

All in all, indirect biomarkers can potentially provide better or complementary information than self-reported alcohol use.

2.1.6 ALCOHOL-RELATED HARM

The negative health, social and economic consequences of alcohol use have been extensively documented. Alcohol use is a leading risk factor of death and disability. Globally, there were almost 3 million deaths attributable to alcohol and 131.6 million disability-adjusted life years (DALYs) lost in 2016 (GBD 2016 Alcohol Collaborators, 2018, Shield, et al., 2020). The majority of deaths (1.74 million) were due to non-communicable diseases (primarily digestive, cardiovascular diseases and cancer), while injuries and communicable diseases (primarily tuberculosis, HIV/AIDS and lower respiratory infections) accounted for 0.87 and 0.36 million deaths, respectively (Shield, et al., 2020).

Alcohol is a necessary cause of 26 health conditions. This means that the condition cannot occur in the absence of alcohol use (e.g. alcoholic liver disease). These include alcohol use disorders, alcoholic liver disease and alcohol intoxication, among others (Rehm, 2011).

In addition, alcohol is a component cause of more than 200 three-digit ICD-10 codes, where alcohol is a risk factor that increases the risk of the condition, but the condition occurs also among non-drinkers (Shield, et al., 2013). These are health conditions where alcohol has been shown to causally increase the risk of the outcome (e.g. colon cancer), but it is not the sole attributable cause nor a necessary cause. Large comparative risk assessment studies (such as the Global Burden of Disease study) commonly use population attributable fractions (PAFs) to estimate the relative contribution of the risk factor (i.e. alcohol). Wholly attributable conditions are assigned a PAF of 1 (i.e. all events are attributable to alcohol). Partly attributable conditions are assigned PAFs between 0 and 1 depending on available evidence. Table 2 includes a non-exhaustive list of wholly and partly alcohol-attributable health conditions, their respective ICD codes and PAFs.

Volume and patterns of alcohol use (see section 2.1.2) affect health and society through three mechanisms. First, direct toxic and biochemical effects that contribute to the development of chronic diseases, such as liver disease, cardiovascular disease and cancer. Second, risky patterns of alcohol use result in intoxication, leading to acute conditions such as accidents and injuries. Third, patterns and volume of alcohol use result in dependence, which leads to chronic disease as well as acute and chronic social consequences (Rehm, et al., 2017).

The toxic and biochemical effects include the direct toxicity of alcohol on cells and tissues and the carcinogenic effect of alcohol and its metabolites, as well as the indirect effects by, for example, increasing blood pressure, reducing immunological response capacity or inducing hormonal dysregulation (Osna and Kharbanda, 2016, Ratna and Mandrekar, 2017).

Alcohol intoxication results from the acute consumption of large amounts of alcohol on a single occasion. Alcohol is rapidly absorbed from the gastrointestinal tract, reaching a maximum blood alcohol concentration after 10 to 60 minutes (Rao and Topiwala, 2020). As a highly-soluble small molecule, alcohol is passively diffused in and out of cells (Bjork and Gilman, 2014). In severe forms, alcohol intoxication *per se* can lead to life-threatening consequences, including respiratory depression, hypothermia, hypotension and tachyarrhythmias (Vonghia, et al., 2008). However, acute alcohol consumption is also associated with severe health consequences at lower levels of alcohol use. Neurotoxic effects include lack of coordination, impaired judgment, prolonged reaction time and behavioural changes (Rao and Topiwala, 2020). These effects

increase the risk of domestic violence, car crashes (when drink driving), various types of injuries as well as fights and assaults (Vonghia, et al., 2008).

Table 2. Health conditions wholly and partly attributable to alcohol

Wholly attributable conditions[1]	**ICD-10 code**	**PAF (%)**
Alcohol-induced pseudo-Cushing's syndrome	E244	100
Mental and behavioural disorders due to use of alcohol	F10	100
Degeneration of nervous system due to alcohol	G312	100
Epileptic seizures related to alcohol	G4051	100
Alcoholic polyneuropathy	G621	100
Alcoholic myopathy	G721	100
Alcoholic cardiomyopathy	I426	100
Alcoholic gastritis	K292	100
Alcoholic liver disease	K70	100
Alcohol-induced acute pancreatitis	K852	100
Alcohol-induced chronic pancreatitis	K860	100
Maternal care for (suspected) damage to fetus from alcohol	O354	100
Fetus and newborn affected by maternal use of alcohol	P043	100
Fetal alcohol syndrome (dysmorphic)	Q860	100
Finding of alcohol in blood	R780	100
Toxic effect of alcohol	T51	100
Accidental poisoning by and exposure to alcohol	X45	100
Intentional self-poisoning by and exposure to alcohol	X65	100
Poisoning by and exposure to alcohol, undetermined intent	Y15	100
Evidence of alcohol involvement determined by blood alcohol level	Y90	100
Evidence of alcohol involvement determined by level of intoxication	Y91	100
Partly attributable conditions[2]		
Tuberculosis	A15-19, B90	18.3
HIV/AIDS	B20-24	3.0
Lower respiratory infections	J09-22, P23, U04	3.2

Cancer of lip and oral cavity	C00–08	31.3
Other pharyngeal cancers	C09–10, C12–14	34.9
Oesophagus cancer	C15	19.3
Colon and rectum cancers	C18–21	11.7
Liver cancer	C22	12.2
Breast cancer	C50	7.2
Larynx cancer	C32	22.3
Diabetes mellitus	E10–14 (minus E10.2–10.29, 1.29, E12.2, E13.2–13.29, E14.2)	-2.2
Epilepsy	G40–41	12
Hypertensive heart disease	I10–15	7.4
Ischaemic heart disease	I20–25	2.7
Ischemic stroke	G45–46.8, I63–63.9, I65–66.9, I67.2–67.848, I69.3–69.4	-2.1
Intracerebral haemorrhage	I60–62.9, I67.0–67.1, I69.0–69.298	9.7
Cardiomyopathy, myocarditis, endocarditis	I30–33, I38, I40, I42	6.6
Cirrhosis of the liver	K70, K74	46.9
Pancreatitis	K85–86	24.4
Unintentional injuries	V01–X40, X43, X46–59, Y40–86, Y88, Y89	18.3
Intentional injuries	X60–Y09, Y35–36, Y870, Y871	16.1

PAF Population attributable fractions (i.e. to alcohol use) 1. Source of ICD-10 codes: World Health Organization, 2019, ICD-10 codes Z502, Z714, Z721 have occasionally been used, but are not recommended to WHO for primary mortality coding. 2. Source of ICD-10 codes and PAFs: Shield, et al., 2020. PAFs based on global estimates for all ages using 2016 data.

Dependence is related to the neurobiological mechanisms that contribute to sustaining drinking. As a clinical entity, dependence can lead to an alcohol use disorder (AUD), a psychiatric disorder characterised by loss of control over alcohol intake, compulsive alcohol use and a negative emotional state when not drinking (Carvalho, et al., 2019). The 4th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), which was in use between 1994 and 2013, included two distinct alcohol use disorders (American Psychiatric Association, 1994): alcohol abuse and alcohol dependence. As described in Table 3, alcohol abuse in DSM-IV was defined as having one or more criteria in four domains (hazardous alcohol use; social or interpersonal problems related to use; neglected major roles to use; and legal problems).

Alcohol dependence was defined as fulfilling three or more criteria out of six (withdrawal; tolerance; used larger amounts/longer; repeated attempts to quit or control use; time spent using; physical or psychological problems related to alcohol use; and giving up activities in order to use).

Table 3. DSM-IV and DSM-5 criteria for alcohol use disorder

DSM-IV	**DSM-5**
Two separate diagnoses (alcohol abuse and alcohol dependence).	One single diagnosis that combines the previous two into one. Moderate and severe AUD are defined according to the number of criteria fulfilled.
Any AUD: Either alcohol abuse or dependence Alcohol abuse: 1 or more alcohol abuse criteria fulfilled. Alcohol dependence: 3 or more dependence criteria fulfilled.	Any AUD: The presence of at least two criteria Mild: 2-3 criteria fulfilled. Moderate: 4-5 criteria fulfilled. Severe: 6 or more criteria fulfilled.
Abuse criteria	
Drinking or recovering from drinking interfered with family, school or job obligations.	Drinking or recovering from drinking interfered with family, school or job obligations.
Alcohol drinking resulted in hazardous situations (injuries, traffic accidents, unsafe sex, etc).	Alcohol drinking resulted in hazardous situations (injuries, traffic accidents, unsafe sex, etc).
Being arrested, held at the police station or had legal problems because of drinking.	This criteria was deleted.
Continued to drink despite interpersonal problems.	Continued drinking despite interpersonal problems.
Alcohol dependence criteria	
Tolerance, drinking more to obtain the same effect or less effect from the usual number of drinks.	Tolerance, drinking more to obtain the same effect or less effect from the usual number of drinks.
Withdrawal symptoms (trouble sleeping, shakiness, restlessness, nausea, sweating, racing heart or seizure).	Withdrawal symptoms (trouble sleeping, shakiness, restlessness, nausea, sweating, racing heart or seizure).
Drinking more or longer than intended.	Drinking more or longer than intended.
Spent great deal of time drinking or recovering from the effects of drinking.	Spent great deal of time drinking or recovering from the effects of drinking.
Given up on important activities because of drinking.	Given up on important activities because of drinking.
Continued to drink despite feelings of depression, anxiety, health problems or memory blackouts.	Continued to drink despite feelings of depression, anxiety, health problems or memory blackouts.
-	Alcohol craving, wanting to drink so badly could not think of anything else

Source: American Psychiatric Association, 1994, 2013

The 5th edition of the DSM (DSM-5), introduced in 2013, integrated alcohol abuse and alcohol dependence into a unidimensional single disorder and introduced a severity sub-classification (mild, moderate and severe) (American Psychiatric Association, 2013). DSM-5 also dropped legal problems and include a new craving criterion (Hasin, et al., 2013).

AUD is the most prevalent substance use disorder, with 100.4 million estimated cases worldwide (Degenhardt, et al., 2018). AUD is a significant contributor to years of life lost and disability: in 2010 it accounted for 44.4% of all years of life lost and 7.9% of DALYs due to mental disorders (Whiteford, et al., 2013). In the 2016 update, AUD accounted for 10% of the DALYs lost due to mental and substance use disorders (Rehm and Shield, 2019). Alcohol use is also associated with vast social and economic harm, affecting not only individuals, but also their families, communities and societal wellbeing as a whole. For individuals, alcohol use is associated with negative social consequences including lower work performance and higher rates of sickness absence (Schou and Moan, 2016, Thørrisen, et al., 2019). The harm to others from alcohol (AHTO) is well documented. In the United States, 20.8% of women and 23% of men have been exposed to AHTO, experiencing harassment or threats, ruined property or vandalism, physical aggression, harms related to driving or financial or family-related problems (Nayak, et al., 2019). Research from ten countries worldwide concluded that generally men are more affected by harms from strangers' drinking, while gender differences in harm caused by family members, relatives and others known to the respondent varied greatly from one country to another (Room, et al., 2019). The consumption of alcohol during pregnancy can lead to foetal alcohol syndrome, a severe condition affecting almost 120,000 children per year worldwide (Popova, et al., 2017).

The economic consequences of alcohol use have been estimated to account for 0.5% to 5.4% of the gross domestic product (GDP) (Barrio, et al., 2017, Ranaweera, et al., 2018, Rehm, et al., 2009, Thavorncharoensap, et al., 2009). Economic impacts are due to indirect causes (mainly from premature death and loss of productivity) and direct costs related to medical and social care, and law enforcement and criminal justice. Other costs included those derived from motor vehicle crashes and property damage (Thavorncharoensap, et al., 2009, Rehm, et al., 2009). In the United States, the economic costs of alcohol use in 2006 (estimated at $223.5 billion US dollars) exceeded largely the revenue from state and federal taxes ($14.6 billion US dollars) (Bouchery, et al., 2011). In Chile, the costs were estimated to be 7.3 times larger than the revenue from alcohol taxes (Departamento de Salud Pública, 2018).

2.2 SOCIOECONOMIC DIFFERENCES IN ALCOHOL USE, DISORDERS AND HARM

Tackling socioeconomic inequalities in health has become an important policy goal in recent decades, both globally and in Finland (Commission on Social Determinants of Health, 2008, Department of Health and Social Security, 1980, Ministry of Social Affairs and Health, 2008). Low socioeconomic status has been consistently associated with higher mortality and lower life expectancy (Lewer, et al., 2020, Mackenbach, et al., 2008) and as a strong contributor of premature mortality (Stringhini, et al., 2017). European countries have generally increased their life expectancy, but progress in reducing socioeconomic differences in mortality has been uneven (Mackenbach, et al., 2019). Nordic countries, despite their universal and generous welfare states, have experienced the least narrowing of inequalities in mortality compared to other European countries. Relative inequalities in mortality have increased in Finland, Sweden, Denmark and Norway for both men and women between 1990 and 2015 (Mackenbach, et al., 2019). A central question of this thesis is to describe and explore potential explanations for the systematic socioeconomic differences in alcohol-related harm, which contrast with the observed socioeconomic differences in alcohol use. In addition, we describe socioeconomic differences in AUDs, one of the most prevalent alcohol-attributable conditions. This is important as can shed light into the stage where these SES differences emerge over the lifecourse. Marked SES differences in AUDs suggest that there are mechanisms influencing the differential incidence of AUDs, while the lack of SES differences in AUDs suggest that differences in survival could play a larger role.

In this section, I review the literature on socioeconomic differences in alcohol use, alcohol use disorders and alcohol-attributable harm. The terms socioeconomic differences, inequalities or disparities are often used interchangeably in the literature to refer to a descriptive account of the differences between socioeconomic groups (Regidor, 2004). The term socioeconomic inequities, however, has a moral connotation and is used to express differences that are considered unfair or unjust (McCartney, et al., 2019, Whitehead and Dahlgren, 2006). Socioeconomic status refers to a "person's position in a hierarchical social structure, encompassing notions of class, status and power" (Bosworth, 2018). Education, income and occupation have been historically the most commonly used indicators of SES (Adler and Newman, 2002), as they relate to a person's access to social and economic resources (Duncan, et al., 2002).

2.2.1 ALCOHOL USE

Researchers have examined the socioeconomic differences in alcohol use extensively over several decades. A summary of these results is shown below.

Abstinence. Lower socioeconomic status has been generally shown to be associated with higher levels of abstinence in both women and men. This has been described since the 1960s in the United States, Finland and other European countries (Cummins, et al., 1981, Department of Health, 1971, Midanik and Clark, 1994, van Oers, et al., 1999). The GENACIS study examined fifteen participating countries (13 European plus Brazil and Mexico) in the early 2000s (Bloomfield, et al., 2006). Using logistic regression models, the study showed that both women and men with low education had higher odds for abstinence than those of high education in most of the examined countries (Bloomfield, et al., 2006). An update with 33 countries using individual-participant data meta-analysis showed that men with low education had 50% higher odds to be abstainers compared to those with high education (OR 1.5, 95% CI 1.3; 1.7) (Grittner, et al., 2013). These educational differences in abstinence were higher in high-income countries (HICs) than lower and middle-income countries (LMICs). The authors observed a similar pattern for women, but the inequalities were higher (OR 2.0, 95% CI 1.8; 2.2) (Grittner, et al., 2013). Heterogeneity was high in all analyses.

More recent studies have confirmed these findings in OECD countries, South Africa and other African countries (Allen, et al., 2018, Probst, et al., 2018, Sassi, 2015). In Germany, a recent longitudinal study showed that higher socioeconomic status was associated with drinking prevalence (i.e. not abstinent) across age, periods and cohorts (Pabst, et al., 2019). Conversely, a recent systematic review in LMICs found higher levels of abstinence among people of higher SES in countries in Southeast Asia (India and Nepal) and Benin (Allen, et al., 2018).

In Finland, there was no evidence of socioeconomic differences in abstinence in the GENACIS study (using data from 2000) (Bloomfield, et al., 2006). The update in 2012 re-analysed the data combining middle and high educational groups. The study found that men and women with middle and high education had higher odds of alcohol use in the past 12 months than those with low education (OR 2.1, 95% CI 1.1; 3.9 in men, OR 2.1, 95% CI 1.1; 4.0 in women) (Grittner, et al., 2013). A OECD study also found that alcohol abstinence was more prevalent among lower socioeconomic groups in both men and women in Finland (concentration index -0.05 and -0.09, respectively) (Sassi, 2015). A recent study on 15-year-olds showed that those with lower education aspirations (used as a proxy of SES) were more often

abstainers in both boys and girls and for the whole study period (1990 to 2014) (Liu, et al., 2016).

Volume of alcohol use. Studies examining volume of alcohol use have reported mixed findings. The GENACIS study and research in Germany, the United States and Australia did not find evidence of differences between socioeconomic groups (Bloomfield, et al., 2000, Bloomfield, et al., 2006, Giskes, et al., 2011, Karriker-Jaffe, et al., 2012). Similar findings were reported in a study of 11 EU countries, were lower educated people showed higher odds of heavy volume drinking only among men in Ireland and Portugal, but evidence was inconclusive in the other countries and for women in all countries (Cavelaars, et al., 1997). In Estonia, participants with basic education or less consumed on average 26 more grams of pure alcohol per week (95% CI 7; 46) compared to those with high education (Parna, et al., 2010). Similarly, in the Stockholm Public Health Cohort, manual workers had a higher prevalence of heavy drinking than higher non-manual employees (Landberg, et al., 2020, Sydén, et al., 2017). Likewise, in the Netherlands, a study from the 1990s showed that men in the lowest educational quintile had higher odds of heavy volume drinking, while the study reported no educational differences in heavy volume drinking for women (van Oers, et al., 1999). In New Zealand, different indicators of SES showed different pictures: higher income was associated with higher frequency of drinking, but not with higher quantity consumed per occasion, while lower education was associated with higher frequency of drinking only at age 18 (and not at age 21 and 26), and was associated with higher quantity consumed per occasion (Casswell, et al., 2003).

Conversely, in OECD countries, higher educated women were more likely to drink higher volumes of alcohol than those with lower education. In men, the picture was more complicated: the magnitude of socioeconomic differences was small and in 8 out of 14 countries men with low education were more likely to report high volume drinking and the rest showed no differences or the opposite (Sassi, 2015). In a recent US study, higher education was consistently associated with higher volume of alcohol use (Lui, et al., 2018). In the United Kingdom, higher socioeconomic groups were more likely to exceed the recommendations for weekly volume, but lower socioeconomic groups were more likely to report very heavy volume and episodic drinking (Lewer, et al., 2016).

Regarding beverage-specific differences, a study in the UK found that those from deprived small-areas had higher odds of typically drinking beer and spirits and lower odds of typically drinking wine (Bellis, et al., 2016).

In Finland, the GENACIS study did not find evidence of socioeconomic differences in heavy volume drinking (Bloomfield, et al., 2006). Similar findings were reported in a study using national survey data from 1994 to 2006 (Parna, et al., 2010). An OECD study found that men and women of higher education were more likely to be heavy drinkers in 2007. In a long-term repeated cross-sectional analysis, Helakorpi et al. (2010) showed that the proportions of moderate and heavy drinkers increased between 1982-1985 and 2004-2008 in all educational groups, but the rise was higher for those with low and intermediate education, reducing the socioeconomic differences over time. Similar findings were observed for women, although differences by SES were not as pronounced (Helakorpi, et al., 2010).

Two studies have explored whether the association between socioeconomic status and alcohol volume and drinking frequency are causal. Both studies used Mendelian Randomization, a type of instrumental variable design, to identify causal effects and they were both carried out with data from the UK Biobank (Rosoff, et al., 2019, Zhou, et al., 2019). An increase in educational attainment was associated with higher alcohol volume, frequency, and higher consumption of wine (red wine, white/champagne and fortified wines). Higher educational attainment was associated with lower consumption of beer and spirits (Rosoff, et al., Zhou, et al., 2019). However, the UK Biobank is based on volunteers and it is not representative of the UK population (Fry, et al., 2017). These results, therefore, might not be generalizable to the general population and other settings.

Heavy episodic drinking. Evidence on socioeconomic differences in heavy episodic drinking is equally mixed. In men, several studies have found that those with lower education have higher frequency of heavy episodic drinking (Giskes, et al., 2011, Harper and Lynch, 2007, Midanik and Clark, 1994, Paljärvi, et al., 2012, van Oers, et al., 1999). The GENACIS study found that lower education was associated with higher odds of HED. This pattern was statistically significant for low education (versus high education) in Norway, Italy, Austria, Hungary, Czech Republic and Israel (Bloomfield, et al., 2006). The update in 33 countries (see above) showed that higher education was associated with lower odds of HED for all countries combined, but the result was only statistically significant in HICs (HICs OR 0.89, 95% CI 0.80; 0.99 and LMICs OR 0.90, 95% CI 0.69; 1.17) (Grittner, et al., 2012). In an OECD study, in most OECD countries men with lower education were more likely to report HED. However, these reversed when using a different SES measure (i.e. either income or occupational class), and men of lower SES were less likely to report HED in ten out of 17 countries (Sassi, 2015). Using data from the World Health

Survey (2002-2004) in 48 countries, a study showed that men of lower education had higher rates of HED in middle-income countries, but lower rates of HED in lower-income countries using both absolute and relative measures of inequality (Hosseinpoor, et al., 2012).

In women, several studies have not found evidence of socioeconomic differences in HED (Bloomfield, et al., 2006, van Oers, et al., 1999). Analysis of data from the World Health Survey (2002-2004) in 48 countries did not find evidence of absolute or relative socioeconomic differences among women in either low or middle-income countries (Hosseinpoor, et al., 2012). Other studies have shown higher frequencies of HED among women with higher education (Giskes, et al., 2011). The GENACIS study found no evidence of socioeconomic differences in HED, except in Brazil where higher educated women had higher odds of reporting HED. The update in 33 countries showed that in LMICs women with high education had higher odds of reporting HED (OR 1.6, 95% CI 1.1; 2.2), while the study did not find evidence of socioeconomic differences in HICs (Grittner, et al., 2013).

In Finland, Paljärvi et al. found that, using several indicators of SES, lower socioeconomic groups experienced higher odds of weekly intoxication in both men and women. For example, women currently unemployed had 2.3 times higher odds of intoxications (OR 2.3, 95% 1.7; 3.0) than those currently employed and without a history of unemployment (Paljärvi, et al., 2012). Exploring long-term trends, another study showed that HED increased sharply among men in the lowest educational group from 2001-2003 to 2004-2008, resulting in a higher prevalence of HED among lower educational groups compared to those with intermediate or higher education. Among women, HED was more prevalent in lower educational groups and remained relatively stable during the study period, while those with intermediate and high education increased their prevalence by about 5 percentage points (Helakorpi, et al., 2010).

Studies in adolescents in Brazil and Spain have shown that those of lower socioeconomic status had lower rates of HED (Jorge, et al., 2018, Martins, et al., 2020, Obradors-Rial, et al., 2018). However, in Norway, adolescents with low educated parents had higher risk of intoxication (Pape, et al., 2018).

Finally, one Mendelian Randomization study showed that an increase in educational attainment was causally associated with lower frequency of HED (β_{IVW} = –0.198, 95% CI –0.297; –0.099) (Rosoff, et al., 2019).

Comparability limitations. Comparability of research results is hampered by several methodological difficulties. First, the comparison of data collected in different years can be

subject to secular trends (changes over time) and cohort effects. For instance, a repeated cross-sectional study in Finland showed that those with highest education (in both men and women) had higher rates of heavy drinking in the 1980s, but those differences almost disappeared in men and reduced considerably in women in the 2004-2008 period. The authors speculate that these differences are a result of a reduction in alcohol taxes in 2004 (Helakorpi, et al., 2010). Reductions have also been reported in socioeconomic differences in alcohol abstinence in Sweden, which the authors attribute to a reduction of alcohol use in the oldest cohorts (Combes, et al., 2011).

Comparisons within and between countries are also sensitive to the choice of socioeconomic indicator, as described above in the study from New Zealand (Casswell, et al., 2003). Different socioeconomic indicators can show different magnitudes of the association (e.g. Paljärvi, et al., 2012) or even a change in the direction of the association. For example, in the OECD study, lower education was associated with higher HED, but lower income was associated with lower HED in Australia (Sassi, 2015).

There are, finally, methodological limitations in the use and reporting of results of logistic regressions (the most common method used) for the study of socioeconomic differences. First, odds ratios overestimate the effect size of the association between two variables when (a) the outcome variable is common (frequency usually higher than 0.2) and (b) odds ratios are high, which is the case with several measures of alcohol use (Davies, et al., 1998, Regidor, 2004). Second, comparing extreme socioeconomic groups (which is often done in the literature on socioeconomic inequalities in alcohol use) has the shortcoming that the relative size of the group affects the size of the measure; the ratio increases if the groups are smaller. This can affect the comparison of different national units with different distributions of the socioeconomic indicator and also secular trends, where e.g. the level of education increases (Cummings, 2009, Khang, et al., 2008, Mackenbach and Kunst, 1997, Manor, et al., 1997, Valkonen, 1993).

2.2.2 ALCOHOL USE DISORDERS

Socioeconomic differences in prevalence of AUD have been examined in several studies. In the United States, evidence from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) showed that people with low education, low income and high poverty levels had a higher prevalence of 12-month AUD in both 2001-2002 and 2012-2013 (Grant, et al., 2017). Using discrete-time survival analysis, a study using NESARC 2001-2002 data showed

that people with any education lower than university education had higher odds for 12-month alcohol dependence, after adjusting for other socio-demographic indicators and age at first alcohol use (Gilman, et al., 2008). In the National Comorbidity Survey Replication (NCS-R), lower education was associated with higher risk of alcohol abuse among regular alcohol users (low education compared to high education OR 3.3, 95% CI 2.2; 4.8), but not with higher odds of alcohol dependence among alcohol abusers (Kalaydjian, et al., 2009). Lower education was, however, associated with higher odds of lifetime substance use disorder in analyses of the same survey (Kessler, et al., 2005). In the National Alcohol Survey, neighbourhood disadvantage was not associated with alcohol dependence after adjusting for individual socio-demographic characteristics (Karriker-Jaffe, et al., 2012).

European studies have shown a mixed picture. In the European Study of the Epidemiology of Mental Disorders (ESEMeD) in ten countries in Europe, unemployed persons had higher odds of prevalent 12-month AUD than those working, but there was no evidence of socioeconomic differences using education and income as SES indicators (Pinto-Meza, et al., 2013). In Norway, people with low education (high school) did not have higher odds of any 12-month substance use disorders than those with more than high school education (Kringlen, et al., 2001). On the contrary, in Germany those of low socioeconomic status (based on an index derived from income, education and occupation) had higher odds of any substance use disorder (Jacobi, et al., 2014). Regarding severity and prognosis, a Swedish study found no evidence that people with low education had higher odds of fulfilling more criteria of alcohol dependence (i.e. a proxy for severity) than those of higher education (Andréasson, et al., 2013). In a register study in Sweden, high parental education was associated with lower risk for onset of AUDs compared to those with low parental education (Kendler, et al., 2016).

In Finland, analyses from the Health 2000 Survey reported that people with high education had higher odds of active alcohol dependence compared to those with primary education (OR 1.6, 95% CI 1.0; 2.6) (Pirkola, et al., 2006). Another Finnish study in young adults aged 21-35 years showed that participants with less than high school education had a much higher prevalence of substance use disorders than those with high school education (24.6% versus 5.9%, respectively) (Latvala, et al., 2009). In addition, lower cognitive ability (a strong correlate of one's income and education) was associated with alcohol misuse events (Latvala, et al., 2016).

An Australian study did not find evidence of differences in 12-month AUD by education or employment status. Unemployed individuals had higher odds of lifetime AUD compared to those employed (Teesson, et al., 2010). In LMICs, a study in São Paulo, Brazil, showed that low

education was associated with higher odds of alcohol dependence among abusers (OR 6.3, 95% CI 1.3; 29.3) and abuse among regular users (OR 3.4, 95% CI 1.4; 7.8) (Silveira, et al., 2011). Another study in Brazil (in Rio Grande) using the AUDIT score as a proxy for alcohol dependence reported that people of low social class had higher odds of potential AUD than those of high social class (Mendoza-Sassi and Béria, 2003). Finally, a study in Shanghai and Beijing, China, did not find evidence of educational differences in the transitions from regular users to alcohol abuse and alcohol abuse to alcohol dependence (Lee, et al., 2009).

All in all, the evidence on the association between socioeconomic status and AUD appears to be inconsistent in most settings. Comparability is limited due to the use of different indicators of socioeconomic status and definitions of the outcome measure.

Change over time in socioeconomic differences in AUD has been, to my knowledge, examined in only one study. Comparing NESARC 2001-2002 and 2012-2013, Grant et al. found that the prevalence of AUD increased for all educational and income groups, yet educational and income differences remained similar between survey periods. For example, prevalence of AUD was 15.2% among those with less than high school education and 12.2% in those with high school education in 2001-2002 and increased to 18.7% and 16.7% in 2012-2013, respectively (Grant, et al., 2017).

2.2.3 ALCOHOL-ATTRIBUTABLE MORBIDITY AND MORTALITY

Several observational studies and systematic reviews dating back to the 1980s have examined the socioeconomic differences in alcohol-attributable morbidity and mortality. Given that non-participation in population health surveys can lead to underestimations of these differences (see section 2.1.3), this section describes separately studies carried out in the whole population (based on census and registers) and those from population health surveys.

Register-based studies. Most of the earlier studies were based on census data linked to mortality data or delinked mortality and census data (Table 4). Using occupation as a socioeconomic indicator, unemployed men in Finland had a 5.2 higher alcohol-attributable mortality than those employed (95% CI 4.2; 6.5) (Martikainen, 1990). Similar findings were described in Sweden, were unemployed men had a higher risk of liver cirrhosis and alcohol dependence, psychosis and intoxication compared to the whole population (Ågren and Romelsjö, 1992). Manual workers (among men) and manual workers and low-level non-manual

workers (among women) had higher risk of hospitalizations due to alcohol dependence, psychosis and intoxication than the whole population (Romelsjo and Lundberg, 1996).

Unskilled male manual workers in Finland had 2.2 times higher rates of alcohol-attributable mortality and 7.5 times higher rates of mortality due to alcohol poisonings than non-manual workers (Valkonen, 1993). Similar results were found with census data from 1985 and 1990: unspecialized male manual workers had 4.1 higher rates of alcohol-attributable mortality compared to upper non-manual workers, while unspecialized female manual workers had 2.4 higher rates than upper non-manual workers (Mäkelä, 1999). In England, male manual workers aged 25-39 years had 15 times higher alcohol-attributable mortality than non-manual workers, while it was 3.2 times higher for the same group aged 55-64. Occupational differences for women were small. Interestingly, female manual workers aged 55-64 had lower mortality compared to non-manual counterparts (RR 0.3, 95% CI 0.2; 0.5) (Harrison and Gardiner, 1999). In Sweden, manual male workers had 3.8 times higher alcohol-attributable mortality and manual female workers had 2.4 times higher alcohol-attributable mortality than their non-manual counterparts (Hemström, 2002). Smaller socioeconomic differences were found in Stockholm county, where manual workers had 87% higher alcohol-attributable mortality than non-manual workers (Norström and Romelsjö, 1998).

Using education as the socioeconomic indicator, a study in Finland found that men had higher educational differences in alcohol-attributable mortality than women; such differences were considerably larger in alcohol poisonings (Koskinen and Martelin, 1994). Another Finnish study showed that alcohol-attributable mortality increased sharply among those with basic education among men and women between 1987 to 2003 (Herttua, et al., 2007). These trends exacerbated after the reduction of alcohol taxes in 2004 (Herttua, et al., 2008). In Russia, educational differences in alcohol-attributable mortality were the second highest among men (after infectious diseases) and the highest among women (Shkolnikov, et al., 1998). In Estonia, educational differences in liver cirrhosis and alcohol poisonings widened between 1990 and 2000 among women and decreased among men (Leinsalu, et al., 2003). Lower education was associated with higher alcohol-attributable mortality in Estonia and Switzerland (Faeh, et al., 2010, Rahu, et al., 2009).

Income has also been used as a socioeconomic indicator. In Finland, alcohol-attributable mortality increased 9.4% by each decile down the income ladder among men and 6.0% among women (Martikainen, et al., 2001). A more recent study in Finland showed a gradient where lower income was associated with higher alcohol mortality (Tarkiainen, et al., 2016).

Importantly, these socioeconomic differences have increased over time. In 1988, the lowest income quintile had 2.8 higher odds of alcohol-attributable mortality than the highest income quintile (95% CI 2.6; 3.0), which increased to 6.5 times higher odds in 2007 (95% CI 5.3; 7.9) (Tarkiainen, et al., 2016). A study in Canada showed that lower income was associated with higher alcohol-attributable mortality (Tjepkema, et al., 2013).

Using area-deprivation as a socioeconomic indicator, a study in Scotland showed a sharp increase in alcohol-attributable causes of death between 1980-1982 and 2000-2002. Among men, the 2000-2002 rates of chronic liver disease and alcohol-attributable mental disorders were 16 times and 22 times greater in the most deprived area than in the least deprived one (Leyland, et al., 2007).

A comparison of 22 countries in the late 1990s and early 2000s showed that Hungary, Lithuania and Estonia had the highest absolute inequalities in alcohol-attributable deaths (Mackenbach, et al., 2008). A more recent study confirmed than in all 17 countries examined, people of lower SES had higher rates of alcohol-attributable mortality. Socioeconomic differences were higher in Eastern European countries, as well as Finland and Denmark, and had increased primarily due to the rise among lower socioeconomic groups (Mackenbach, et al., 2015).

One study examined the socioeconomic differences in alcohol-related hospitalizations, comparing partly and wholly alcohol-attributable conditions. The results showed much greater socioeconomic differences for wholly alcohol-attributable chronic and acute conditions than partly attributable conditions (Sadler, et al., 2017).

Table 4. Register-based studies on socioeconomic differences in alcohol-attributable mortality

Study	Country	Design	Main findings
Martikainen, 1990	Finland	Census data (1980) linked to mortality data from 1981-1985. Analysis were restricted to men 30- 55 years old.	Unemployed men showed the highest relative mortality compared to those employed (adjusted RM 5.2, 95% CI 4.2; 6.5).
Ågren and Romelsjö, 1992	Sweden	Census data (1970) linked to mortality data until 1980.	Compared to the rate of the whole population (reference), unemployed men had the highest risk of liver cirrhosis and AAA (alcohol dependence, psychosis and intoxication). Among women, several white-collar occupations had lower liver and AAA mortality, but no occupational group showed statistically significant higher RRs, likely due to the few deaths per occupational group.
Valkonen, 1993	Finland	Census data (1970, 1975 and 1980) linked to mortality data.	Educational and occupational differences in all-cause mortality widened in Finland from 1970 to 1980. Male unskilled blue-collar workers had 2.2 times higher rates of alcohol-related mortality and 7.5 times higher mortality due to alcohol poisonings than white-collar men.
Koskinen and Martelin, 1994	Finland	Census data (1980) linked to mortality data from 1981-1985.	Educational differences in alcohol mortality were higher for men and women (Index of dissimilarity 5.4 in men and 4.1 in women). Differentials were much larger for alcohol poisonings (14.5 and 4.2 for men and women respectively).
Romelsjö and Lundberg, 1996	Sweden	Census data from 1970, 1975, 1980 and 1985 linked to mortality data.	Compared to the rate of the whole population (reference), unemployed men and women had higher rate ratios of AAA mortality (e.g. 1980-1984 Men RR 10.2, 95% CI 9.4; 11.0; Women RR 7.1, 95% CI 6.0; 8.4). Similar results were described for AAA hospitalizations, except manual workers (among men) and manual workers and low-level non-manual employees (women) had higher risk.
Mäkelä, et al., 1997	Finland	Census data (1985 and 1990) linked to mortality data from 1987-1990 and 1991-1993.	In men, alcohol deaths account for 14% of the excess mortality between manual workers and upper non-manual workers and 24% of the difference in life expectancy. Excess mortality due to accidents and violent deaths was 49%. In women, differences were smaller.

Norström and Romelsjö, 1998	Sweden (Stockholm county)	Census data (1990) linked to mortality data from 1991-1995.	Manual workers had a relative risk of 1.9 of alcohol-attributable mortality compared to non-manual workers.
Shkolnikov, et al., 1998	Russia	Mortality counts in 1979 and 1989 divided by census data from 1979 and 1989.	Educational differences in alcohol mortality were the highest compared to other causes of death among women (RR 4.6) and second after infectious diseases in men (RR 3.7).
Harrison and Gardiner, 1999	England, Wales and Scotland	Census data from 1980 to 1995 linked to mortality data until 1995.	Alcohol-related mortality rates were higher for men aged 25-39 (RR 15.0, 95% 9.7; 23.4) in the manual occupations than in the non-manual occupations and also in men aged 55-64 (RR 3.2, 95% CI 2.6; 4.1). There was no evidence of occupational differences for women aged 25-39 (RR 1.5, 95% 0.8; 2.8) and differentials were inverse for women aged 55-64 (RR 0.32, 95% CI 0.2; 0.5).
Mäkelä, 1999	Finland	Census data (1985 and 1990) linked to mortality data from 1987-1990 and 1991-1993.	Among men, unspecialized manual workers had a mortality rate ratio of 4.7 and 3.6 for acute and chronic causes compared to upper white-collar workers. Specialized manual workers had a RR of 3.0 and 2.5 for acute and chronic causes, respectively. Among women, there was practically no difference.
Martikainen, et al., 2001	Finland	Census data from 1990 linked to mortality from 1991-1995.	Alcohol-attributable mortality increases by 9.4% and 6.0% by each decile down the income ladder from highest to lowest in men and women respectively.
Hemström, 2002	Sweden	Census data from 1980 and 1990 linked to mortality data from 1990-1995.	Manual workers had 3.2 times higher alcohol mortality rate than non-manual workers (RR 3.2, 95% CI 2.9; 3.5) among men and 2.4 times higher among women (RR 2.4, 95% CI 2.0; 2.9).
Leinsalu, et al., 2003	Estonia	Mortality counts from 1987-1990 and 1999-2000 divided by census data from 1989 and 2000.	Mortality from alcohol liver cirrhosis and alcohol poisoning increased sharply in Estonia from 1990 to 2000 and educational differences widened. Men with lower secondary education had 2.1 times higher mortality due to alcoholic liver cirrhosis than those with university education (RR 2.2, 95% CI 0.8; 6.2) in 1989 and 1.7 times higher in 2000 (RR 1.7, 95% CI 1.0; 2.8). Among women, those with lower secondary education or less had 1.6 times higher mortality in 1989 (RR 1.6, 95% CI 0.2; 14.3) and 5.5 times higher in 2000 (RR 5.5, 95% CI 1.6; 18.7).

Herttua, et al., 2008	Finland	National mortality data from 2001-2003 and 2004-2005 linked to employment statistics.	Men with basic education had a 3.5 relative rate of alcohol-attributable mortality than those with upper tertiary education (RR 3.5 95% CI 3.1; 4.0). Women with basic education had a 4.1 relative rate of alcohol-attributable mortality than their counterparts with upper tertiary education (RR 4.1 95% CI 3.0; 5.8). The reduction in alcohol taxes affected disproportionately people with secondary and basic education and unskilled workers, both men and women.
Mackenbach, et al., 2008	22 European countries	Mortality data	Alcohol-attributable deaths accounted for 11% of inequalities in mortality among men and 6% among women. Absolute inequalities in alcohol-attributable deaths were higher in Hungary (420), Lithuania (304) and Estonia (286) for men. Absolute inequalities among women were smaller but were higher in Estonia (101), Lithuania (87) and Hungary (82).
Rahu, et al., 2009	Estonia	Case-control comparing cases (alcohol-attributable deaths) with controls (cancer deaths without substantial SES differences).	Lower education was associated with higher mortality odds of alcohol-attributable deaths. Women with basic education or lower had the highest odds (MOR 4.9, 95% CI 3.8; 6.4) compared to those with higher education.
Faeh, et al., 2010	Switzerland	Census data from 1990 and 2000 linked to mortality data from 1990 to 2000.	Lower education was associated with higher alcohol-attributable mortality in both men and women and both German and French-speaking Switzerland.
Tjepkema, et al., 2013	Canada	15% sample of 1991 census data linked to mortality data. 75% successful linkage.	Alcohol-related mortality was 3.8 times higher for the lowest income quintile compared with the highest income quintile.
Mackenbach, et al., 2015	17 European countries	National and regional register data linked to mortality data or unlinked cross-sectional data	People of lower SES had higher rates of alcohol-attributable mortality. Socioeconomic differences in alcohol-attributable mortality were higher in Eastern European countries, as well as Finland and Denmark and have increased primarily due to the rise among lower socioeconomic groups.
Sadler, et al., 2017	England	Hospital admissions in England for the period 2010-2013.	Socioeconomic inequalities for alcohol-related admissions were higher for wholly-attributable conditions. The relative index of inequality for wholly-attributable acute conditions was 6.8 for men and 3.6 for women, and 5.7 and 2.5 for wholly-attributable chronic conditions in men and women, respectively.

RM Relative mortality RR Relative risk MOR Mortality odds ratio CI Confidence interval

Survey-based studies. Survey-based studies described in Table 5 were based on cohorts of general population, public sector employees, conscripts and other population groups.

In Finland, a study on municipal employees found that compared to those with permanent jobs, women with temporary jobs and the unemployed had 66% and 5.5 times higher risk of alcohol-attributable mortality, respectively. Men showed similar patterns (Kivimäki, et al., 2003). Similar findings were described in a cohort of unemployed people in Danzig, Poland (Zagozdzon, et al., 2008). A study in Sweden was inconclusive on the association between unemployment and alcohol-attributable mortality (Voss, et al., 2004). Another study in Stockholm county in Sweden found that skilled and unskilled manual workers both had 4.1 times higher alcohol-attributable events (i.e. deaths and hospitalizations) than higher non-manual workers (Sydén, et al., 2017). In the same cohort, manual workers had also a higher risk of short and long-term sickness absence than non-manual workers (Landberg, et al., 2020). In a study of Swedish conscripts born 1949-1951, education, income and occupational class were strongly associated with alcohol-attributable mortality (Falkstedt, et al., 2013).

In a cohort of 25-54 years old men in Izhevsk, Russia, lower education and being a widower, divorced or never married were associated with higher alcohol-attributable mortality (Pridemore, et al., 2010). In a study in the general population in Scotland, lower socioeconomic groups experienced between 3.7 and 5.2 times higher alcohol-attributable events, depending on the socioeconomic indicator used (Katikireddi, et al., 2017).

Table 5. Survey-based studies on socioeconomic differences in alcohol-attributable mortality

Study	Setting	Design	Main findings
Rossow and Amundsen, 1996	Norway	33,224 Norwegian conscripts examined in 1951-1952. Followed up until 1990.	Liver cirrhosis deaths were higher in the groups of academic professionals than unskilled and skilled workers (7.5 and 6.0 per 100,000 person-years).
Kivimäki, et al., 2003	Finland	85,271 municipal employees in 10 Finnish cities from 1990 to 2000 and 7,080 unemployed people who obtained a subsidized contract in the mentioned cities. Linked to mortality data until 2001 (1,332 deaths; 414 were alcohol-attributable).	People with temporary jobs and unemployed had higher all-cause and alcohol mortality. Compared to those with permanent jobs, unemployed men and those with temporary jobs had 3 times and 97% higher risk of alcohol deaths (HR 3.1, 95% CI 2.0; 4.5 and HR 2.0; 95% CI 1.4; 2.9) respectively. Similar differences were found for women (corresponding estimates were HR 5.5, 95% CI 3.4; 8.9 and 1.7, 95% CI 1.1; 2.5).
Voss, et al., 2004	Sweden	18,516 women and 18,020 men Swedish twins born between 1926 and 1958 and interviewed by mail questionnaire in 1973; linked to mortality data.	Unemployment was not statistically associated with higher alcohol mortality in both men and women, primarily due to the low number of events.
Kivimaki, et al., 2007	Finland	18,042 men and 47591 women working in 10 Finnish municipal governments from 1994 to 2001 linked to mortality data until 2001 (179 alcohol-related deaths).	Lower educated men showed higher alcohol-related mortality than those with tertiary education (HR 1.6, 95% CI 1.1; 2.5). Female manual workers had higher risk of alcohol-related mortality than upper non-manual workers (HR 2.2, 95% CI 1.1; 4.0 respectively).
Zagozdzon, et al., 2009	Poland	47,247 unemployed men and women registered at the Danzig City and Danzig County between 1999 and 2004; linked with mortality data over the same period.	Unemployment was associated with higher risk of alcohol-related mortality in both men and women (total RR 2.9, 95% CI 2.3; 3.7). The risk ratio was similar for men and women (RR 2.9 vs 2.8).
Hart, et al., 2010	Scotland	6,022 men and 1,006 women employed in factories and workplaces; linked to mortality data.	Manual workers were more likely to be heavy drinkers and smokers. 21% of men were smokers and heavy drinkers. Heavy drinkers and smokers had higher alcohol-related mortality than other drinking/smoking combinations.

Pridemore, et al., 2010	Russia	Izhevsk Family Study. Cases were male 25-54 years old who died between 2003 and 2005. Controls were randomly selected males from 2002 (1,750 cases and 1,750 controls).	Lower education and being widower, divorced or never married were strongly associated with higher alcohol-related mortality. Alcohol consumption and smoking accounted for around 50% of these differences.
Falkstedt, et al., 2013	Sweden	49,321 Swedish male conscripts in 1969/1970 linked to mortality data from 1991 to 2008.	Alcohol-attributable mortality showed the highest inequality of measured causes of death. The HRs varied from 6.0 to 11.4 for education, occupation and income.
Sydén, et al., 2017	Sweden	18,035 participants aged 25-64 in the Stockholm Public Health Cohort interviewed in 2002 and followed up until 2007 for either alcohol hospitalization or death.	Unskilled manual workers and skilled manual workers had higher risk of alcohol-attributable events (i.e. hospitalizations and death) than higher non-manual workers (HR 4.1, 95% CI 2.8; 6.0 and 4.1, 95% CI 2.7; 6.3) in a basic model adjusted for sex, age and country of birth.
Katikireddi, et al., 2017	Scotland	50,236 participants in the Scottish Health Surveys 1995-2012 linked to hospitalization, prescriptions and mortality data.	Socioeconomic status was associated with higher alcohol-attributable events for all socioeconomic indicators used: no education vs degree or above (HR 3.8, 95% CI 3.0; 4.8), most deprived versus least deprived (HR 3.7, 95% CI 2.9; 4.6), unskilled manual worker versus professional (HR 5.2, 95% CI 3.3; 8.3), and lowest versus highest income quintile (HR 4.4, 95% 3.1; 6.3). All models were adjusted for sex, age and survey wave.
Pagh Møller, et al., 2018	Denmark	National school-based cross-sectional study.	There were no clear differences in alcohol use by parental SES. Lower parental SES was associated with higher risk of alcohol related harm (being in a fight or accident, had problems with parents or friends, had sex or drugs and regretted afterwards due to alcohol), the magnitude of the differences was small.
Landberg, et al., 2020	Sweden	17,008 participants aged 25-64 in the Stockholm Public Health Cohort interviewed in 2006 and followed up until 2008 for long-term sickness absence.	Male manual workers had 73% higher risk of short-term sickness absence (RR 1.73 95% CI 1.5; 1.9) and 4.0 times higher risk of long-term absence than non-manual employees (RR 4.0 95% CI 2.3; 6.9). Corresponding estimates in women were 1.4 (95% CI 1.3; 1.6) and 2.4 (95% CI 1.8; 3.3).

HR Hazard ratio RR Relative risk CI Confidence interval

Systematic reviews. Two related systematic reviews have appraised the available evidence on socioeconomic differences in alcohol-attributable mortality. In 2014, Probst et al. compared socioeconomic differences in alcohol-attributable mortality with all-cause mortality, showing that lower socioeconomic status was associated with 78% higher mortality (RRR 1.78, 95% CI 1.4; 2.2) for alcohol-attributable causes than all-cause mortality among men and 66% higher among women (RRR 1.66, 95% CI 1.20; 2.31) (Probst, et al., 2014. Another review explored gender differences in alcohol-attributable mortality. Socioeconomic status was associated with higher alcohol-attributable mortality in both men and women. For example, low education was associated with 2.9 times higher risk of alcohol-attributable mortality among men and 2.7 times higher among women. Relative risks were highest according to employment status, followed by income, education and occupation, even though the heterogeneity was high for all indicators (Probst, et al., 2015).

All in all, the evidence from both register-based and survey-based studies consistently shows that lower socioeconomic status is associated with higher alcohol-attributable mortality.

2.3 THE ALCOHOL-HARM PARADOX

The most obvious explanation for the socioeconomic differences in alcohol-attributable harm would be differential exposure to alcohol use, i.e. due to systematic differences in alcohol use between socioeconomic groups. However, the observed socioeconomic differences in alcohol use appear insufficient to explain the socioeconomic gap in alcohol-attributable harm. This discrepancy between the socioeconomic differentials in alcohol use and harm has been called "the alcohol harm paradox".

The term "alcohol harm paradox" was first coined by British scholars in 2015 (Bellis, et al., 2016, Jones, et al., 2015, Jones, et al., 2015), but the topic has been a subject of investigation since the 1990s (Mäkelä, 1999). Research on potential explanations for socioeconomic differences in alcohol-attributable mortality dates back from the 1980s (Martikainen, 1990, Valkonen, 1993).

Figure 2 presents potential explanations for the alcohol harm paradox. The figure illustrates potential mechanisms that could explain the association between socioeconomic status and alcohol-related harm that are not caused by differential exposure to alcohol use. For parsimony,

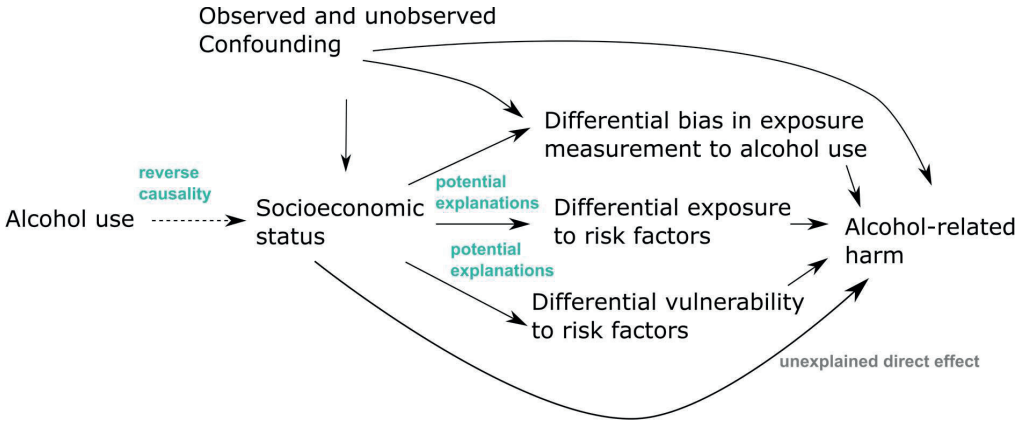
however, the figure does not intend to be a formal directed acyclic graph, where the potential explanations might be disentangled into a complex web of causal connections. These explanations of the alcohol harm paradox in the literature can be broadly categorised into three groups (Figure 2):

(i) Differential biases in the measurement of alcohol use

(ii) Differential vulnerability to risk factors other than alcohol use

(iii) Reverse causality

Figure 2. Explanations for the alcohol harm paradox



In the next sections (2.3.1-2.3.3), I discuss the different hypothetical explanations proposed. In section 2.4, the empirical evidence available of the existence of the alcohol harm paradox and for these explanations is discussed in detail.

2.3.1 DIFFERENTIAL BIASES IN THE MEASUREMENT OF ALCOHOL USE

The alcohol harm paradox could arise from differential biases in the measurement of alcohol use. We discuss four potential biases in the measurement of exposure to alcohol: unidimensional assessment, measurement error, selection bias and drinking trajectories. To provide an explanation to the alcohol harm paradox, these biases in the measurement of exposure need to be systematically different across socioeconomic groups.

Unidimensional assessment refers to the assessment of a single dimension of alcohol use, rather than as a multidimensional concept. As described in section 2.1.2, both drinking volume and patterns matter for alcohol related-harm, and thus the paradox could be explained by socioeconomic differences in patterns of alcohol use, rather than in differences in overall alcohol use, such as volume intake. Quality of alcohol is another dimension to consider in certain settings. The consumption of adulterated alcoholic beverages, home-produced, or nonbeverage alcohols (e.g. eau-de-colognes or medicinal tinctures) might pose a risk of methanol poisoning, which is associated with toxic effects and even death (Gil, et al., 2009, World Health Organization, 2014). This has been well-described in Russia (Leon, et al., 2007), but there have also been reports of methanol poisoning outbreaks in countries with robust alcohol quality assurance systems, such as Norway and Estonia (Hovda, et al., 2005, Paasma, et al., 2007).

The second potential bias is measurement error. Evidence discussed in sections 2.1.4 shows that population health surveys capture only a fraction of the true alcohol consumption measured from more reliable sources such as alcohol sales (Livingston and Callinan, 2015). This is partly explained by several types of information bias (described in section 2.1.4) including recall, social desirability and top-coding bias. Again, the alcohol harm paradox can arise from differential information bias by socioeconomic groups.

A third potential bias is selection bias (see section 2.1.3). Selection bias, as discussed above, might arise from the sampling frame to select the participants (e.g. web surveys might exclude older adults, household surveys might exclude people living in institutions) or from non-participation of, for example, heavy substance users or people with severe mental disorders (Jousilahti, et al., 2005, Tolonen, et al., 2006). For example, people with a disability pension due to AUD or substance use disorders had 8.9 times higher risk of non-participation in a Norwegian study (Knudsen, et al., 2010).

Finally, cross-sectional surveys might fail to capture drinking histories or trajectories. Alcohol use starts on average during adolescence, increases during the earlier twenties and subsequently decreases when people take adult roles (Berg, et al., 2013, Maggs and Schulenberg, 2004). Life events, such as divorce, widowhood or retirement can trigger changes in alcohol use (Halonen, et al., 2017, Kendler, et al., 2017). Therefore, a survey carried out at one time point may not be able to distinguish these different drinking histories. Longitudinal studies with repeated measures on the same individuals provide a better account of drinking trajectories. Such data exists for birth or population cohorts (e.g. the Northern Finland Birth Cohort 1966 and 1986 in Finland), although nationally representative longitudinal studies are less common.

2.3.2 DIFFERENTIAL VULNERABILITY TO RISK FACTORS

Risk factors can influence social inequalities in health through differential exposure and differential vulnerability (Hussein, et al., 2017). Individuals in lower socioeconomic groups are more often exposed to many different personal and environmental risk factors other than alcohol use. These personal and environmental risk factors deteriorate their health, which makes them more vulnerable to many types of diseases and risks, including alcohol-attributable harm. Lower socioeconomic groups might also experience differential vulnerability, which refers to differences in the effects of similar levels of risk factors across socioeconomic groups and the capacity to respond to harmful exposures or external shocks (Blas and Kurup, 2010, Diderichsen, et al., 2018). This explanation suggests that joint effects between alcohol and risk factors could result in disproportionately greater levels of alcohol-attributable harm for people in lower socioeconomic groups.

In high-income economies, lower socioeconomic status is generally associated with higher levels of smoking (Clare, et al., 2014, Gilman, et al., 2003), obesity (McLaren, 2007) and physical inactivity (Gidlow, et al., 2006). Lower socioeconomic groups may also have poorer quality diets. People of lower SES might not be able to afford a healthy diet, not have appropriate access to healthy food or be more heavily exposed to marketing of ultra-processed, unhealthy products (Darmon and Drewnowski, 2008, Fagerberg, et al., 2019, Pechey and Monsivais, 2016).

Lower socioeconomic groups could be more likely to drink in unsafe settings, such as neighbourhoods with higher criminality and violence (Fabio, et al., 2011), as well as with less developed public infrastructure, such as traffic lights and pedestrian crossings (Hart, 2015, Schmidt, et al., 2010). As a result, lower socioeconomic groups might experience higher risks of acute consequences of alcohol use deriving from violence (assaults, homicides) and traffic accidents even for similar levels of alcohol use.

People of lower SES might be more exposed to chronic stress and also have a lower capacity to buffer the effects of harmful exposures or shocks. Low socioeconomic status has been linked to higher levels of psychological stress (Talala, et al., 2008), and stressful life events (Baum, et al., 1999, Christiansen, et al., 2020, Lantz, et al., 2005), which could potentially mediate the relationship between socioeconomic status and alcohol-attributable harm. Evidence suggests that socioeconomic status might be associated with differential methylation of several gene promoter regions (Needham, et al., 2015, Stringhini, et al., 2015). Such differential methylation could hamper the ability of a cell to respond to a specific exposure or stressor, increasing the susceptibility to further exposure to the same stressors (Cunliffe, 2016). A related explanation is

cumulative disadvantage, which suggests that, over the lifecourse, socioeconomic disadvantages might accumulate and multiply (Mäkelä, 1999).

Another potential mechanism of differential vulnerability is through constraints in access to health care and social resources. Studies suggest that people of lower SES experience lower survival of alcoholic liver disease (Jepsen, et al., 2009) and lower rates of liver transplantation (Liu, et al., 2019). There are several potential explanations for the differential access to health care, including geographical restrictions, financial barriers due to out-of-pocket payments, acceptability barriers related to stigma, cultural appropriateness of health services and ability to argue and require an adequate level of care (Keyes, et al., 2010, Probst, et al., 2014, Steele, et al., 2007).

Given that alcohol use is a necessary cause for alcohol-attributable harm (i.e. it cannot occur in the absence of alcohol use), differential vulnerability as an explanation of the alcohol harm paradox is conceptualized as joint (or interactive) effects between alcohol use and these potential explanatory factors. In addition, the existence of joint effects between SES and these potential explanatory factors (e.g. SES and smoking) most likely does not have a causal interpretation, but it probably reflects selection, i.e. individuals with a certain risk factor, smokers for example, tend also to have higher levels of alcohol use and other risk factors (Sydén, et al., 2017). This interaction is, hence, most probably capturing unmeasured alcohol use or indirectly the interactive effect between alcohol and the explanatory factor.

2.3.3 REVERSE CAUSALITY

Differential bias in the measurement of exposure and differential vulnerability provide a possible explanation for the causal effect of socioeconomic status on alcohol-attributable harm. In other words, they could represent mechanisms mediating the relationship between SES and alcohol-related harm.

An alternative explanation is reverse causality, where alcohol use causally affects socioeconomic status (Katikireddi, et al., 2017, Makela, et al., 2015). In this explanation, alcohol use might negatively impact educational attainment in early adulthood, affect income and/or employment status in later stages of life (Mäkelä, 1999, Mullahy and Sindelar, 1989). Recently, a study in Sweden and Finland showed that people who died of an alcohol-attributable cause experienced a substantial decline in income for a long period of time, suggesting that extensive alcohol use might negatively impact the income level of people of low SES (Tarkiainen, et al.,

2019). Another longitudinal study in Finnish and Swedish young adults showed that HED was subsequently associated with unemployment, but not vice versa (i.e. unemployment was not associated with subsequent HED) (Berg, et al., 2017). Early onset of problem drinking was also associated with subsequent higher unemployment rates and less months employed in Finland (Paljärvi, et al., 2015).

2.4 EMPIRICAL EVIDENCE OF THE ALCOHOL HARM PARADOX AND POTENTIAL EXPLANATIONS

2.4.1 THE EXISTENCE OF THE ALCOHOL HARM PARADOX

As discussed in section 2.2.3, the existence of socioeconomic differences in alcohol-attributable harm has been the subject of extensive research since the 1980s. These earlier studies contrasted the results of register-based studies on socioeconomic differences in alcohol-attributable harm with other studies exploring socioeconomic differences in alcohol use in the same country.

In recent years, however, the existence of the alcohol harm paradox has been described in the same population group (i.e. datasets that have data both on alcohol use and harm). In a Swedish study, unskilled workers had 4.1 times higher risk of alcohol-attributable events than higher non-manual employees, but differences in the prevalence of heavy drinkers were not as stark (14.5% in unskilled workers vs 12.4% in higher non-manual employees) (Sydén, et al., 2017). In a Scottish study, participants in the lowest income quintile experienced 4.4 times higher risk of alcohol-attributable events than subjects in the highest income quintile, but reported similar rates of excessive drinking (4.4% in the lowest income quintile vs 4.6% in the highest income quintile) and lower rates of heavy episodic drinking (15.0% vs 25.5%) (Katikireddi, et al., 2017). Similarly, in a Finnish study, manual workers had 2.1 times higher risk of alcohol-attributable events compared to non-manual workers, but the prevalence of consuming more than 10 litres of pure alcohol per year was not very different (8.5% in manual workers vs 6.9% in non-manual workers) (Mäkelä and Paljärvi, 2008).

Evidence also suggests the existence of joint effects between socioeconomic status and alcohol use. The aforementioned study in Scotland showed joint effects between all SES indicators and alcohol use on alcohol-attributable events. For example, excessive drinkers with high income had a HR of 5.4 (95% CI 3.4; 8.4) of alcohol-attributable mortality compared to

never or former drinkers, while the corresponding figure for excessive drinkers with low income was 8.7 (95% CI 5.5; 13.8) (Katikireddi, et al., 2017). Similarly, Mäkelä et al. in Finland found that the risk of alcohol-attributable harm was disproportionately higher among manual workers in the highest consumption category and HED category (Mäkelä and Paljärvi, 2008).

Using additive hazard models, a Danish study showed that men with low education and high alcohol use experienced 289 extra events per 10,000 person-years due to the additive interaction (95% CI 123; 457), while women experienced an excess of 239 extra deaths due to the additive interaction per 10,000 person-years (95% CI 90; 388). Overall, these results suggest that increased alcohol use is associated with disproportionately higher risk of alcohol-attributable harm.

In the next sections, empirical studies that examined explanatory mechanisms of the socioeconomic differences in alcohol-attributable mortality and the alcohol harm paradox are reviewed. We considered both studies that have examined potential explanations of the socioeconomic differences in alcohol-attributable harm and the few studies analysing the causes of the alcohol harm paradox. Most previous studies are mediation analyses where authors compare the change in estimate for the SES indicator (i.e. the attenuation of the SES differences) after adjusting for potential explanatory factors. We restrict the presentation to longitudinal studies with alcohol-attributable harm as an outcome. Studies solely reporting the socioeconomic differences in alcohol use, alcohol use disorders or alcohol-attributable harm have been described in sections 2.2.1-2.2.3. Table 6 presents a summary of the studies reviewed in the following sections.

Table 6. Previous studies examining explanatory factors of socioeconomic differences in alcohol-attributable harm and the alcohol harm paradox

Author, year	Setting	Measure of SES	Main findings
Mäkelä, 1999	Finland, census data from 1985 and 1990. Follow-up until 1987-1990 and 1991-1995 respectively.	Educational level	In minimally-adjusted models, low educated men and women experienced a 3.3 times and 3.0 times higher risk of alcohol-attributable death than people with high education, respectively (p-value < 0.01). Adjusting for all SES indicators attenuated the rate ratio of low educated persons compared to those with high education to 1.4 (95% CI 1.3; 1.6) among men and to 1.9 (95% CI 1.5; 2.3) among women for the same comparison groups described before.
Mäkelä, et al., 2003	Finland, register linked data 1991-1996. Follow-up until 31 Dec 1997	Occupational class	Unspecialised manual workers had a 3.6-fold rate of alcohol-related hospitalizations compared to upper white-collar workers, among men, and 2.7-fold rate among women. There were no differences in survival after the hospitalization by occupational class.
Voss, et al., 2004	Sweden, all same-sex twins born 1926-1958 and who completed a self-administered questionnaire in 1973. Follow-up until December 31, 1996.	Employment status	In age-adjusted models, men and women with long-term unemployment had a 2.0 and 1.3 relative risk (95% CI 0.8; 4.8, 95% 0.2; 11.0, respectively) of alcohol use disorder, liver cirrhosis or pancreatitis deaths compared with those never unemployed. Adjusting for age, marital status, smoking status, alcohol use, use of tranquilizers/sleeping pills and long-lasting/serious illness resulted in a relative risk of 1.3 (95% 0.5; 3.3) among men and 1.0 (0.1; 8.1) among women.
Mäkelä & Paljärvi, 2008	Finland, Finnish Drink Habits Surveys, 1969-1984. Follow-up was for 16.3 years at each baseline survey.	Occupational class	In minimally-adjusted models, manual workers showed a hazard ratio of 2.1 (95% CI 1.4; 3.0) compared to non-manual workers. Adjusting for alcohol use and drinking patterns explained approximately 15% of the excess hazard among manual workers. There was evidence of additive (and not multiplicative) joint effects between socioeconomic status and alcohol use.

Pridemore, et al., 2010	Russia, Izhevsk Family Study case-control study. Only male participants.	Educational level	In crude models, men with incomplete secondary education had 6.4 times higher odds of alcohol-attributable mortality than those with complete higher education (95% CI 3.4; 11.8). Adjusting for age, hazardous drinking, smoking status and marital status resulted in an OR of 1.2 (95% CI 0.5; 2.7) of those with incomplete secondary education compared with those with complete higher education.
Tarkainen, et al., 2016	Finland, register data from 1988, 1994, 2001 and 2007. Follow-up for 6-year periods from the baseline year.	Household income	In the age-adjusted model, men in the lowest income quintile had higher odds of alcohol-attributable mortality than those in the highest income quintile (range from 2.8 in 1988 to 6.5 in 2007). The corresponding association in women was 2.1 in 1988 and 8.0 in 2007. Adjusting sequentially for education, occupational class and economic activity resulted in attenuations of 51-57% among men and 32-69% among women.
Nordahl, et al., 2017	Denmark, Social Inequality in Cancer (SIC) cohort study. Follow-up until 31 Dec 2009.	Educational level	There was evidence of joint effects between education and alcohol use on alcohol-attributable events. In men, the joint effect of low education and high alcohol use resulted in 289 extra events (alcohol hospitalizations and deaths) due to the interaction (95% CI 123; 457). In women, the joint effect of low education and high alcohol use resulted in 239 extra events due to the interaction (95% CI 90; 388).
Katikireddi, et al., 2017	Scotland, Scottish Health Surveys, 1995-2012*	Educational level Social class Income Scottish Index of Multiple Deprivation	There were marked socioeconomic differences in alcohol-attributable harm for all four measures of socioeconomic status. Adjustment for alcohol use and HED had little effect on the estimates. Associations attenuated slightly after adjusting for smoking and obesity. There was evidence of joint effects between socioeconomic status and alcohol use on alcohol-attributable events. There was little evidence of reverse causation.
Sydén, et al., 2017	Sweden, Stockholm Public Health Cohort, 2002. Follow-up until 31 Dec 2011.	Occupational class	In minimally-adjusted models, unskilled workers showed a hazard ratio of 4.1 (95% CI 2.9; 6.0) of alcohol-attributable events compared to higher non-manual employees. Adjusting for HED resulted in an attenuation of 25% of the HR, while adjusting for a combined measure of alcohol use (volume and pattern) attenuated the HR by 24%. Further adjustment for behavioural, social, material factors and educational factors reduced the HR by 59%.

HED Heavy episodic drinking HR Hazard ratio OR Odds ratio. Alcohol-attributable events refers to a combined outcome of alcohol-attributable hospitalization and mortality. * Follow-up date not described

Attenuations described are based on change in coefficients

2.4.2 DIFFERENTIAL BIAS IN THE MEASUREMENT OF ALCOHOL USE

Three studies have examined the role of drinking patterns as an explanation for the alcohol harm paradox. One study in Sweden found that after adjusting for heavy episodic drinking, the hazard ratio of alcohol-attributable harm attenuated by 25% (initial HR was 4.1 and attenuated to 2.9). Similar results (attenuation of 24%) were found when using a combined measure of alcohol use (volume and pattern) (Sydén, et al., 2017).

A Scottish study found that adjusting for both volume of alcohol use and heavy episodic drinking resulted in marginal attenuations of the hazard ratio of alcohol-attributable harm for education and occupational class. For example, the HR of those with no education compared to the highest educational level attenuated from 3.8 (95% CI 3.0; 4.8) to 3.4 (95% CI 2.6; 4.5). Likewise, the HR increased after adjusting for alcohol volume and HED when using income or area-based deprivation as SES indicators (Katikireddi, et al., 2017).

Similarly, Mäkelä and Paljärvi in Finland showed that adjusting for alcohol volume and drinking patterns resulted in a marginal attenuation of the HR of manual workers compared to non-manual workers. The HR attenuated from 2.1 (95% CI 1.4; 3.0) to 1.9 (95% CI 1.3; 2.8), approximately a 15% reduction. The authors found similar results using different measures of drinking patterns (Mäkelä and Paljärvi, 2008).

All in all, these results suggest that drinking patterns explain a small fraction of the association between socioeconomic status and alcohol-attributable harm.

2.4.3 DIFFERENTIAL VULNERABILITY TO RISK FACTORS

Two studies have directly examined whether behavioural risk factors could explain the alcohol harm paradox. The Scottish study examined the combined effect of smoking and BMI. The authors adjusted first for alcohol use (volume and patterns) and further adjusted for smoking and BMI. The HRs attenuated for all measures of SES. For instance, the HR for alcohol-attributable harm in the lowest income quintile (compared to the highest income quintile) attenuated from 4.9 (95% CI 3.3; 7.1) to 3.6 (95% CI 2.4; 5.3) (Katikireddi, et al., 2017). In the Swedish study, adjusting for smoking attenuated the HR of alcohol-attributable harm in unskilled workers from 2.9 (95% CI 2.0; 4.3) to 2.4 (95% CI 1.6; 3.6) (Sydén, et al., 2017).

In addition, other studies have tried to explain the SES differences in alcohol-attributable mortality, without adjusting separately for alcohol use. A Swedish study explored whether the association between unemployment and alcohol-attributable mortality attenuated after adjusting

at the same time for sociodemographic factors, smoking, alcohol use, use of tranquilizers and long-lasting illnesses. Unfortunately there were only few (40) alcohol-attributable deaths in the sample and confidence intervals were compatible with a wide range of associations before and after adjustment (Voss, et al., 2004). Another study in Russia examined the effect of adjusting for age, hazardous drinking, smoking status and marital status on the association between education and alcohol-attributable mortality (Pridemore, et al., 2010). The study showed an important attenuation from an OR of 6.4 to 1.2, but since all variables were adjusted at once, it is not possible to disentangle which factors explain the results. These are not direct evaluations of the alcohol harm paradox, as it cannot be ruled out that alcohol use explained the attenuations.

Other studies have examined whether cumulative disadvantage could explain the socioeconomic differences in alcohol-attributable mortality. A Finnish study in the late 1990s showed that adjusting for several indicators of SES resulted in a marked attenuation of the association between education and alcohol-attributable mortality (Mäkelä, 1999). A more recent study in Finland showed that adjusting for education, occupational class and economic activity attenuated by 51-57% the association between income and alcohol-attributable mortality among men and 32-69% among women (Tarkiainen, et al., 2016). In Sweden, adjusting for employment status and income attenuated the hazard ratio of unskilled workers (compared to higher non-manual workers) from 2.9 to 2.1 (31% attenuation) (Sydén, et al., 2017).

Finally, Mäkelä et al. explored whether poor survival among lower socioeconomic groups could explain the socioeconomic differences in alcohol-attributable mortality in Finland. Using register-linked data from alcohol-attributable hospitalizations and alcohol-attributable mortality, the authors did not find differences in survival among occupational classes (Mäkelä, et al., 2003). Most of these studies (except the one in Sweden) did not have information on alcohol use, although based on the evidence on socioeconomic inequalities in alcohol use in Finland (see section 2.2.1), they could be considered indirect evaluations of the alcohol harm paradox.

2.4.4 REVERSE CAUSALITY

In Scotland, Katikireddi et al. examined reverse causality by comparing the change in area-based deprivation across socioeconomic groups. Heavy or excessive drinkers experienced similar rates of downward mobility as light to moderate and never or ex-drinkers. In regression analyses, the authors found evidence of small upward mobility (mean difference relative to non-drinkers 0.06 (95% CI 0.03; 0.09), finding little evidence for reverse causation (Katikireddi, et al., 2017).

2.5 KNOWLEDGE GAPS

The review of the literature established the importance of monitoring and comparing socioeconomic differences in alcohol use, alcohol use disorders and alcohol-attributable harm. Evidence on socioeconomic differences in alcohol use showed mixed results, particularly regarding volume of alcohol use and HED. Comparability between studies is limited by differences in the countries, time periods and socioeconomic indicators used, as well as the common use of logistic regression models (see section 2.2.1). In Sub-study I, we described socioeconomic differences in alcohol use in Finland and Chile using the concentration index, a summary measure that overcomes some of the shortcomings of logistic regression models.

Few studies have described socioeconomic differences in AUD and findings have been mixed. To my knowledge, only one study in the United States has explored changes over time in socioeconomic differences in AUD, showing that prevalence differences between socioeconomic groups existed and remained relatively stable between 2001-2002 and 2012-2013. In Sub-study II, we reported changes in prevalence of AUD in Finland from 2000 to 2011 and changes in socioeconomic correlates.

The review of the literature clearly indicates that there is a large knowledge gap regarding what explains the alcohol harm paradox. In the differential bias in the measurement of alcohol use, no studies have explored whether accounting for measurement error, selection bias or drinking trajectories could explain the paradox. The alcohol biomarkers discussed in section 2.1.2 could be a potential solution to measurement error, as they provide an objective measure of alcohol use and are not subject to information bias.

Differential vulnerability is also largely unexplored. No study has examined whether the joint effects between alcohol and behavioural risk factors such as smoking or BMI or the joint effects between SES and behavioural risk factors could explain the paradox. Traditional mediation analysis cannot fully accommodate situations when there is an interaction between socioeconomic status and alcohol use (i.e. exposure-mediator interactions). Moreover, adjusting for a behavioural risk factor does not allow separating the effect through the mediator (differential exposure) and through the joint effect between SES and the mediator (differential vulnerability). Separating the contribution of differential exposure and vulnerability is important as their policy implications are different (Diderichsen, et al., 2018)

The overall and specific aims of the study are presented below.

3 Aims

The overall aim of this study was to examine the socioeconomic differences in alcohol use and alcohol-related harm and to identify explanatory factors for the alcohol harm paradox in Finland.

The specific aims of the study were:

1. To investigate the existence and patterns of socioeconomic inequalities in alcohol use in Finland and Chile using nationally representative data (Sub-study I)
2. To examine the changes in the prevalence and the socioeconomic correlates of alcohol use disorders between 2000 and 2011 in Finland (Sub-study II)
3. To examine whether the systematic differences in alcohol-attributable mortality in Finland are due to underreporting of alcohol use in surveys versus biomarkers (GGT, CDT, ALT, AST) (Sub-study III)
4. To quantify the extent to which socioeconomic inequalities in alcohol-attributable mortality in Finland are explained by joint effects between alcohol and behavioural risk factors (smoking and body mass index) and between SES and behavioural risk factors (Sub-study IV)

4 Methods

4.1 STUDY DESIGNS

The study design varied for each sub-study. For Sub-study I, the study design was a cross-sectional study of national health surveys in Finland and Chile. For Sub-study II, the design was a cohort study with repeated measurements. For Sub-study III and IV, the design was a cohort study of repeated cross-sectional national health examination surveys linked to the mortality register. We report the study in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) (Vandenbroucke, et al., 2007).

4.2 PARTICIPANTS

Participants were permanent residents in Finland in 2008-2011 (also Chile 2009-2010 in Sub-study I), 2000 and 2011 (Sub-study II) and 1978-2007 (Sub-study III and IV). We used data from nationally representative population health surveys. All Finnish surveys used the Population Register of Statistics Finland as a sampling frame. This is a register of individuals (Finnish and foreign citizens) residing permanently in Finland, including people living in institutions and conscripts (Statistics Finland, 2020). In the case of the Mini-Finland Survey and the Health 2000 Survey, for administrative reasons, a copy hosted at the Social Insurance Institution was used.

Sub-study I used pooled data from the Health Behaviour and Health among the Finnish Adult Population (AVTK). AVTK was a national postal health survey representative of the permanent residents in Finland aged 15 to 64 years old. AVTK was carried out each year from 1978 to 2015 and used a random sampling design to invite 5000 permanent residents in Finland. We pooled data from 2008 to 2011. Selected individuals received a single postal questionnaire (sent during the first week of April on each survey year), which they filled in and returned by mail before July 31 (Helakorpi, et al., 2012). Participation rates ranged from 64.3% (2008) to 55.7% (2011) (Helakorpi, et al., 2012). Table 7 summarises the study participation and analytical samples used in each Sub-study.

Table 7. Participation in the population health surveys used in the study

	Sub-study I		Sub-study II		Sub-studies III[1] and IV		
	AVTK 2008-2011	ENS 2009-2010	Health 2000	Health 2011	Mini-Finland 1978-1980	Health 2000	FINRISK 1982-2007
Sampled/Eligible	20000	7212	8028	8006	8000	8028	64252
Participated in main interview	N/A	5429	6986	4729	7703	6986	24604
Participated in health examination	N/A	5052	6354	4381	7217	6354	45379
Completed self-administered questionnaire	11772	N/A	N/A	N/A	7217	6736	46636
Comparable age range	9994	3477					
Complete data on all variables[2]	9781-9586	3221-3216	6005[3]	4381[3]	7045-7072	6058-6160	39061-40400

1. Some biomarkers in Sub-study III (CDT, AST, ALT) were only available in a subsample (CDT n=7240, ALT n=7758, AST n=7043) 2. The exact number of participants varies depending on the variables included in each analysis. 3. The main analysis in Sub-study II used multiple imputation, which uses all the data available (including incomplete variables).

We also used data from the Chilean Health Examination Survey (ENS 2009-2010). The ENS 2009-2010 was a national health examination survey representative of the Chilean population aged 15 and over. The survey, carried out between 2009 and 2010, used a multi-stage clustered sampling design stratified by region and urban/rural areas, resulting in 29 sampling clusters. The sampling frame was the National Census 2002. The first stage was the selection of municipalities using a systematic probability proportional to population size. The second stage was the selection of small areas (stratified by rural/urban status) using a systematic probability proportional to the number of households. The third stage was the selection of households, which were randomly selected. The fourth stage was the selection of participants, which were randomly selected. People over 65 years old were oversampled (2:1) (Ministerio de Salud, 2014).

Participants aged 15 and over were invited for a home interview carried out by trained interviewers. A second home visit by a nurse or midwife was scheduled for the health examination and a second interview, which included the alcohol questions (Ministerio de Salud, 2014). The participation rate was 70% for the health examination and second interview.

Sub-study II used data from the Health 2000 Survey and Health 2011 Survey. Health 2000 was a national health examination survey representative of the permanent residents in Finland aged 18 and over. Health 2000 used a stratified two-stage cluster sampling design. Finland was divided in five geographical strata (university hospital districts). The first stage involved the selection of 80 health centre districts (clusters) from a total of 249 districts in mainland Finland. Fifteen health centre districts corresponding to the largest towns were selected with a probability of 1. The remaining 65 health centre districts were selected using a systematic probability proportional to population size. The second stage involved the selection of individuals, which was carried out using systematic random sampling. Adults over 80 years old were oversampled (2:1) to ensure a higher precision on estimates of the oldest age groups (Heistaro, 2008).

Participants aged 30 and over (i.e. the data used in this study) were invited for a home interview carried out by trained interviewers. After the home interview, participants filled in a self-administered questionnaire (questionnaire 1) and were invited to a comprehensive health examination. Data were collected between August 2000 and June 2001. Participation rates differ for the different stages of data collection: 88.8% participated in the home interview, 84.4% filled in questionnaire 1 and 79.6% participated in the health examination (Heistaro, 2008).

Health 2011 Survey was the follow-up of the Health 2000 Survey. Members of the Health 2000 Survey sample who fulfilled the inclusion criteria were invited to participate in the Health 2011 Survey. The inclusion criteria were: (i) to be alive and living in Finland in 2011; (ii) to have contact details available; and (iii) to have not refused to participate in further surveys. The sample thus included participants and non-participants in the Health 2000 Survey. Eligible individuals were invited for a health examination and received a self-administered questionnaire to fill in. Unlike the Health 2000 Survey, the health interview was carried out during the health examination. Data were collected between August and December 2011. The participation rate was 59% for the health examination (Lundqvist and Mäki-Opas, 2016).

Sub-study III and IV used pooled data from eight cross-sectional health examination surveys: the Mini-Finland Survey (1978-1980), the FINRISK National Study (1982-2007) and the Health 2000 Survey. The Mini-Finland Survey was a national health examination representative of the Finnish population aged 30 or older. The Mini-Finland Survey (MFS1978-1980) used a stratified two-stage cluster sampling design. The first stage involved the selection of 40 clusters (one municipality or in some cases two neighbouring ones, out of 320 clusters) from 40

geographical strata using a probability proportional to size sample. These 40 strata consisted of eight strata for the largest towns and 32 nearly-equal sized clusters of 40,000-60,000 eligible individuals. The second stage involved the selection of individuals by systematic sampling in each stratum using the register database from the Social Insurance Institution (Aromaa, et al., 1989, Lehtonen and Pahkinen, 2003). Eligible individuals were invited for a home interview by a trained nurse. After the home interview, participants received a letter with a self-administered questionnaire and an invitation to a health examination. The health examination was used as a screening, based on which part of the participants were invited for a clinical health examination. Data were collected between early 1978 and late 1980. Participation rates were overall high: 96.3% participated in the health interview and 90.2% participated in the health examination (Aromaa, et al., 1989).

The National FINRISK study (FINRISK) was a national health examination survey representative of the Finnish adult population primarily aged 25 to 64 years in selected geographical areas. The survey was carried out between 1972 and 2012. We used data from the 1982, 1987, 1992, 1997, 2002 and 2007 survey rounds. The age range of sampled participants varied between the survey years and geographical areas, generally expanding over time and areas of Finland (Table 7). The National FINRISK Study from 1982 onwards used a stratified random sampling design, the sample was stratified by area, sex and 10-year group, drawing equal numbers of men and women across age groups (Borodulin, et al., 2015). We excluded people who participated in more than one independent survey by chance (1448 individuals in total). Eligible individuals were invited to a health examination and received a self-administered questionnaire. Data used in this study were collected during a 3-month period at the beginning of each study year. Participation rates gradually declined from 82.0% in 1982 to 66.6% in 2007 (Borodulin, et al., 2017).

Table 8. Geographical areas and age ranges represented in the National FINRISK Study, 1982-2007

	Survey areas					
Survey year	**1982**	**1987**	**1992**	**1997**	**2002**	**2007**
North Karelia	25-64	25-64	25-64	25-74	25-74	25-74
Northern Savo	25-64	25-64	25-64	25-64	25-64	25-74
Turku and Loimaa	25-64	25-64	25-64	25-64	25-64	25-74
Helsinki and Vantaa	Not included	Not included	25-64	25-74	25-74	25-74
Oulu	Not included	Not included	Not included	25-64	25-64	25-74

Source: Adapted from Borodulin, et al., 2017

4.3 MEASURES

4.3.1 SOCIOECONOMIC STATUS

We used education (Sub-studies I-IV) and income (Sub-studies III and IV) as indicators of SES. We chose education given some of its desirable properties: education (measured either in years or by highest qualification achieved) does not decrease over the life course and it is, therefore, less sensitive to reverse causality. A person's education is an asset generally considered a precondition for high occupational levels and income. Income was used as it reflects a person's purchasing power, which could be more directly related to higher affordability of alcohol use. Another advantage of using income as an indicator of SES is that it can be categorized in balanced groups (e.g. deciles or quintiles) and it is therefore less prone to bias due to changes in the relative sizes of the compared groups. Both education and income can be categorized into ratio scale variables (see below) and can be used in composite measures that include the whole socioeconomic spectrum (O'Donnell, et al., 2008).

Education. For Sub-study I, we used self-reported years of education as the indicator of SES. For the mathematical computation of the concentration index (see section 4.4), the socioeconomic indicator is required to be measured on a ratio scale with three properties: (i) the scale starts from zero; (ii) the difference between the values is equal and (iii) individuals can be

ranked from lowest to highest (O'Donnell, et al., 2008). Years of education fulfills these criteria and was comparable between the two countries examined (Finland and Chile). In AVTK 2008-2011, the question was "How many years have you been in school full-time altogether? Include elementary school" (Helakorpi, et al., 2009). In ENS 2009-2010, the question was "Number of completed educational years (excluding preschool)" (Ministerio de Salud, 2020).

For Sub-study II, we used the highest completed educational level. In the Health 2000 Survey, this is calculated with two questions, one about basic education (with alternatives ranging from "less than primary school" to "matriculation examination (i.e. high school graduation)" and another about the highest completed education after basic education (ranging from "no vocational school at all" to "doctoral degree"). We coded this into three categories: basic (no matriculation examination and at most a vocational course or on the job training), intermediate (high school or completed vocational school) and high (degree from a vocational institution, polytechnic or university) (Heistaro, 2008).

For Sub-studies III and IV, we used the highest completed educational level. We developed a harmonization protocol to obtain comparable indicators of education across surveys, which were coded in three categories: basic, intermediate and high (the harmonization protocol was published in the Supplementary Appendix of Sub-study III).

Income. For Sub-studies III and IV, we used total household income during the past year as the income indicator. All surveys asked for the taxable income (i.e. the income before taxes), but only in the Health 2000 Survey it explicitly included State transfers (e.g. pensions, child and student allowances). All questions were categorical, with 13 categories in Mini-Finland and Health 2000 and nine categories in FINRISK surveys. For the extreme categories, we chose the given lower and upper boundary, for categories in between, we calculated the midpoint range. This value of taxable household income was divided by the number of consumption units (the first adult counts as 1 unit, other adults as 0.7 and children 0.5) and transformed into quintiles within each survey. The exact questions and harmonization method are included in the harmonization protocol.

4.3.2 BEHAVIOURAL RISK FACTORS

Alcohol use. For Sub-study I, we used four indicators of alcohol use: alcohol abstinence, weekly grams of alcohol use, heavy volume drinking and heavy episodic drinking. We assessed alcohol abstinence in Finland and Chile by a question on whether participants have consumed any alcoholic beverages during the past 12 months. We assessed weekly grams of alcohol used in Finland by a question on the number of portions of beer (in 330 cl bottles), long-drink - a Finnish pre-mixed alcopop (in 330 ml bottles), cider or light wines about 5% (in glasses), wine or similar (in glasses) and spirits (in restaurant portions, 40 ml) consumed during the last week. We converted the number of drinks into grams of pure alcohol by multiplying the number of drinks by 12 grams, equivalent to the approximate alcohol content of each of the categories. In Chile, we assessed weekly volume of alcohol use by a question on the amount of beer, wine and similar (chicha and pipeño, two types of unfiltered nouveau wines) and spirits (pisco, ron, whisky, tequila, vodka, gin or other strong liquors) consumed each day during the past week. Participants were handed a card with pictures of portion sizes to assess the volume of each portion. We converted the number of drinks into grams by multiplying the number of drinks by the grams of pure alcohol in each portion size (provided by the Chilean Ministry of Health) for each day of the week (Ministerio de Salud, 2014). We then added all the grams per day into a single weekly measure. We report the population distribution of weekly alcohol use, including abstainers. Heavy volume drinking was a dichotomous variable created after weekly grams of alcohol used. We considered heavy volume drinkers as those participants consuming more than 210 grams of pure alcohol per week in men and 140 grams of pure alcohol per week in women, following the multinational GENACIS study (Bloomfield, et al., 2005). We measured heavy episodic drinking by a question on how often respondents drank 6 or more drinks at a time in Finland and 5 drinks in Chile. We created a dichotomous variable defined as participants reporting HED once a month or more often.

For Sub-studies III and IV, we used weekly grams of alcohol used during an average week. We assessed weekly grams of alcohol used by a question on the number of portions of beer, cider and long drinks (in 330 ml bottles), wine (in 8cl glasses in Mini-Finland, 80 and 120 ml in Health 2000 and 120 ml in FINRISK), and spirits (in 40 ml portions). There were differences in the recall period: Mini-Finland and Health 2000 asked about an average week during the past month and FINRISK asked about the last seven days. More details about the different questions can be found in the harmonization protocol in the Supplementary Appendix of Sub-study III. Given that surveys collected data during a wider range of years (between 1978 and 2007), where

there were changes in the strengths of alcoholic beverages, we estimated the average strength for each type of beverage for each survey year and used these beverage and time specific strengths to convert portions into grams of pure alcohol. We used sales statistics from the Finnish Institute for Health and Welfare for this purpose (Finnish Institute for Health and Welfare, 2009). In Sub-study III, we created a categorical variable with the following categories, drawing on previous studies (Smyth, et al., 2015, Sydén, et al., 2017): never and former drinkers (combined), low intake (>0 to <84 grams of ethanol per week), moderate intake (men 84 to <252 g/wk; women 84 to <168 g/wk), high intake (men 252 to <612 g/wk, women 168 to <432 g/wk) and very high intake (men ≥612 g/wk, women ≥432 g/wk). In Sub-study IV, we combined the high intake group and the very high intake group to increase the internal validity of the comparison group for the joint effects analysis (see below).

In sensitivity analyses for Sub-study III, we used questions available only in Health 2000 and FINRISK to separate never and former drinkers and to adjust for heavy episodic drinking. In sensitivity analyses for Sub-study IV, we used HED as an alternative indicator of alcohol use. More details about how these variables were constructed and harmonized can be found in the Supplementary Appendix of Sub-study III.

Smoking. For Sub-studies III and IV, we assessed smoking status using structured questions on smoking habits. The questions included whether the participants have ever smoked, have ever smoked regularly and whether they smoke at the time of the interview. Each survey had a summary variable created by the survey team. We harmonized this summary variable and created a categorical variable with the following categories: never smoker, former smoker and current smoker.

Body mass index. For Sub-studies III and IV, we used body mass index as an indicator of obesity. In all surveys, weight and height were measured by trained nurses using standard methods. We calculated the body mass index as the weight (in kg) divided by the height (in m) squared. We created a categorical variable using the classification of the World Health Organization: <18.5 underweight, 18.5 to 24.9 normal, 25 to 29.9 overweight, ≥30 obesity (World Health Organization, 1995).

4.3.3 OTHER SOCIO-DEMOGRAPHIC AND HEALTH VARIABLES

We included other socio-demographic and health variables that were used as explanatory variables or as confounders.

Age. For Sub-study I, we categorized age into two categories: 25 to 44 years and 45 to 64 years. For Sub-study II, we categorized age in the following categories: 30 to 44 years, 45 to 54 years, 55 to 64 years, 65 to 74 years and 75 and over. For Sub-studies III and IV, we used attained age (age at baseline) as the timescale (see below). We calculated the exact age by subtracting the date of the health examination from the birth date. The result (in days) was divided by 365.25 to convert it into years.

Sex. Sex was asked as two categories, male and female. We created a categorical variable with these two categories.

Marital status. For Sub-studies II, III and IV, we assessed marital status by a question enquiring on the current marital status. We dichotomized marital status by combining those married and cohabiting versus those single, widowed, separated or divorced.

Self-rated health. For Sub-study III, we assessed self-rated health by a question enquiring the respondent's present state of health with a Likert scale with five possible answers (ranging from good to poor in Mini-Finland and Health 2000 and from excellent to very bad in FINRISK). We dichotomized self-rated health combining the lowest two categories (poor and rather poor) versus the three highest categories (moderate, rather good and good).

Baseline health conditions. For Sub-study III, we assessed several self-reported health conditions by questions on whether the participant has been diagnosed by a doctor to have diabetes, myocardial infarction, stroke, gallstones or emphysema. In Mini-Finland and Health 2000, all questions asked about the lifetime diagnosis ("Has a doctor ever diagnosed you with"). In FINRISK, diabetes, myocardial infarction and stroke were asked for a lifetime ("Has a doctor ever diagnosed you with"), but for gallstones and emphysema, the recall period was 12 months. We coded these questions into dichotomous variables (1=yes, 0=no).

4.3.4 ALCOHOL BIOMARKERS

For Sub-study III, we used the indirect alcohol biomarkers, GGT, CDT, ALT and AST. GGT was available in all surveys (n=52164), while CDT, ALT and AST were available in subsamples. CDT was available in FINRISK 1997 (n=7240). ALT was available in FINRISK 2002 (n=7758). AST was available in Mini-Finland (n=7043). In all surveys, serum GGT was determined using the kinetic method and following international recommendations at the time of the survey. CDT was analysed using the double antibody essay. AST and ALT were measured using the kinetic method. All samples were analysed at the central laboratory of the National Public Health Institute. More details about the laboratory measurements can be found elsewhere (Heistaro, 2008, Järvisalo, et al., 1989, Niemelä, et al., 2017).

4.3.5 ALCOHOL USE DISORDERS

For Sub-study II, the outcome was 12-month and lifetime prevalence of alcohol use disorders. We used the Munich version of the Composite International Diagnostic Interview (M-CIDI). The original CIDI is a structured mental health interview developed by WHO to provide comparable, cross-cultural DSM-IV diagnoses for epidemiological research (Kessler and Ustun, 2004). The Munich version was chosen because, at the time of planning of the Health 2000 Survey, it was the best version available to be applied as a computer-assisted personal interview. The M-CIDI was defined in parallel to the CIDI 2.1 version, responding to a need to provide DSM-IV based diagnoses. The M-CIDI has shown good psychometric properties: the test-retest reliability showed *kappa* values of 0.78 for any alcohol disorder and 0.83 for alcohol abuse (i.e. both considered excellent), in a sample of 60 persons aged 14-24 years old, with a mean interval of 38.5 days between interviews (Lachner, et al., 1998, Wittchen, et al., 1998).

The Health 2000 Survey included six sections of the M-CIDI: anxiety disorders, depressive disorders, mania, schizophrenia and other psychotic disorders and alcohol use disorders and other substance use disorders. The alcohol use disorders module consisted of two parts: part A included questions about volume and patterns of alcohol use, and part B was applied only to participants who have drunk more than 12 times during any one-year period. Part B included a set of more specific questions on alcohol use: those who drink less than 1-24 grams of lifetime weekly alcohol use and never drink alcohol more than two times per week skipped the alcohol dependence section, since it was considered to be highly unlikely they would fulfill alcohol

dependence criteria. They were, nonetheless, asked questions on alcohol abuse. The M-CIDI was applied by a trained nurse during the health examination. Interviewers asked alcohol dependence questions (11 in total) and alcohol abuse questions (11 in total) one by one.

Participants received a 12-month alcohol dependence diagnosis if they had three or more out of seven DSM-IV criteria concurrently during the past 12 months. Alcohol abuse was defined as having one or more of the four DSM-IV criteria concurrently during the past 12 months. Following DSM-IV hierarchy rules, alcohol abuse was not diagnosed when dependence was present (Hasin, 2003). Participants who fulfilled the DSM-IV criteria for alcohol dependence and abuse concurrently over any 12-month period received a lifetime diagnoses of alcohol dependence or abuse. (Pirkola, et al., 2006). We defined alcohol use disorder as having either alcohol dependence or abuse.

The test-retest reliability of the M-CIDI in H2000 was evaluated for depression and dysthymia, showing excellent inter-rater agreement and *kappa* values (Heistaro, 2008).

The Health 2011 Survey included the M-CIDI, but due to time constraints and the experience from H2000, sections on manic disorders and substance use other than alcohol were omitted. The number of questions was also reduced to retain the questions essential for diagnostic algorithms. The alcohol use disorders module experienced two changes: (i) questions on effects and initiation of alcohol use were omitted, and (ii) diagnostic questions for alcohol abuse and dependence were asked from a list instead of sequentially. There were also small changes in the wording of questions (Lundqvist and Mäki-Opas, 2016).

Lifetime hospitalizations for psychiatric disorders (see section 4.4) were linked from the hospitalizations register (HILMO) using the following ICD-10 codes: any psychiatric disorder (F04-F99), alcohol dependence (F10), dementia (F00-F03), other non-affective psychosis (F22-25, F28-29), depressive disorders (F32-33, F341), schizophrenia (F20), anxiety disorders (F40-42, F430, F431).

4.3.6 ALCOHOL-ATTRIBUTABLE MORTALITY

For Sub-studies III and IV, the primary outcome was alcohol-attributable mortality (see section 2.1.6). We defined alcohol-attributable mortality as deaths with any of the following ICD 8, 9 or 10 codes, either as the underlying or a contributory cause of death: ICD-10 F10, G312, G4051, G621, G721, I426, K292, K70, K852, K860, O354, P043, Q860 and X45 for accidental poisonings by alcohol; ICD-9: 291, 303, 3050A, 3575A, 4255A, 5353A, 5710A–5713X, 5770D–

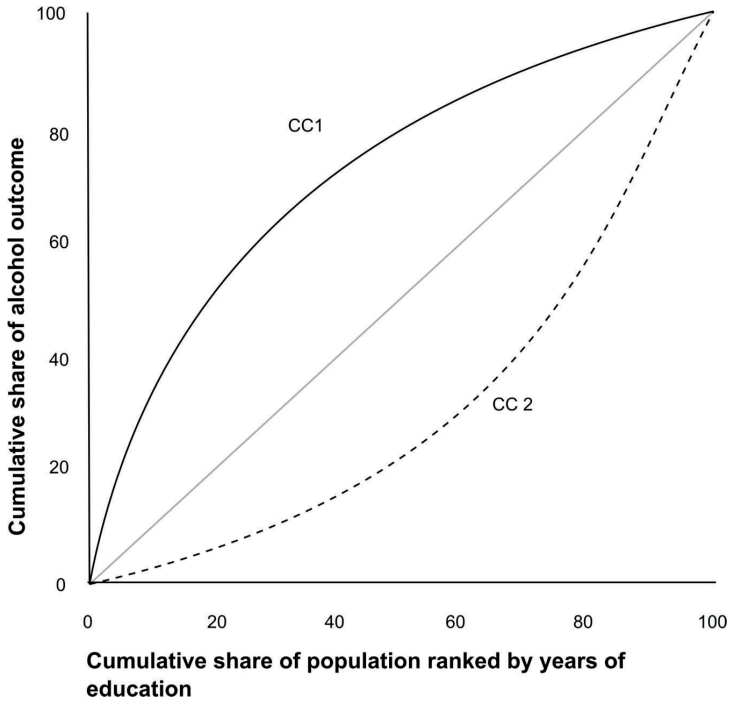
5770F, 5771C–5771D, 7607A, 7795A, 980; ICD-8: 291, 303, 5710, 577 (only for males), 980. Contributory causes of death were available and used since 1987 (Statistics Finland, 2018).

Information on the cause of death was obtained from Statistics Finland. The procedure for the death registration is established in Law 459 (1973) (Ministry of Social Affairs and Health, 1973). Deaths have to be reported immediately to a physician or to the police. The death certificate is completed by a physician, or by a forensic pathologist when a forensic autopsy is performed. All death certificates were reviewed by trained examiners at Statistics Finland, a role that was transferred to the Finnish Institute for Health and Welfare in 2009. Statistics Finland is responsible for the registration (Ministry of Social Affairs and Health, 1973). The quality of death registries has been rated very high, with a very low number of questionable death certificates (Lahti and Penttilä, 2001, 2003, Mikkelsen, et al., 2015). The coverage of death certificates is over 99% (Lahti, 2005) and the proportion of deaths that undergo an autopsy is higher than in other developed countries (Lunetta, et al., 2007).

4.4 STATISTICAL METHODS

Sub-study I. We used the concentration index as a summary measure of the socioeconomic distribution of the alcohol indicator. The concentration index was proposed by Wagstaff in 1991 for the study of socioeconomic inequalities in health and since then it has been extensively used in the fields of health economics and health services research (Wagstaff, et al., 1991). Only recently, there have been studies using the concentration index for the study of socioeconomic differences on behavioural risk factors and NCDs (Zhang and Wang, 2007). The concentration index is calculated in reference to the concentration curve (Figure 3), which plots on the x axis the cumulative distribution of individuals by socioeconomic level and on the y axis the cumulative distribution of the health variable (Regidor, 2004). In Sub-study I, socioeconomic level is the years of education and the health variables are the four indicators of alcohol use. A 45-degree diagonal line represents perfect equality. The concentration index is defined as twice the area between the concentration curve and the line of equality. The concentration index has values between +1 and -1. A value between +1 and 0 indicates that the health indicator is more common in the higher socioeconomic groups, whereas a value between 0 and -1 indicates that the health variable is more common in the lower socioeconomic groups (O'Donnell, et al., 2008).

Figure 3. Concentration curve



CC1 and CC2 represent two concentration curves. CC1 lies above the diagonal axis (line of equality) and therefore means that the alcohol outcome is concentrated among those with lower education. CC2 lies below the line of equality and denotes that the alcohol outcome is concentrated among those with higher education. The concentration index is the area between the line of equality and the concentration curve. Adapted from (Zhang and Wang, 2007).

The computation of the concentration index involves ranking individuals from the lowest to the highest socioeconomic level (Wagstaff, et al., 1991). Using years of education as the socioeconomic variable poses an additional challenge. As repetitive values (i.e. individuals with the same number of years of education) are common, standard methods for calculating the concentration index with microdata can lead to unstable point and variance estimates, depending on how the health variable is sorted (Chen and Roy, 2009). To overcome this challenge, we corrected the fractional rank by giving tied observations an identical fractional rank. This method ensures the sample mean of the fractional rank equals 0.5, allowing the use of standard sample covariance formulas which can incorporate sampling weights (Van Kerm, 2009).

The concentration index was calculated using a covariance-based formulation

$$(1)\ Concentration\ index\ (X,Y)\ =\ -2\,Cov(\frac{X}{\mu(X)},(1-G(Y)))$$

where X is the health variable divided by the sample mean and $G(Y)$ is the cumulative distribution of the socioeconomic variable Y (i.e. years of education).

The limits of the concentration index from -1 to +1 described above apply for continuous variables. For binary outcomes (i.e. heavy volume drinking and HED), the limits are not -1 and +1, but $\mu(X)-1$ and $1-\mu(X)$. To account for this, we used a solution proposed by Wagstaff consisting of dividing the concentration index by $1-\mu(X)$ to obtain a normalized value with limits -1 and +1 (Wagstaff, 2011).

Sub-study II. We reported model-adjusted prevalences (adjusted for sex and age) of AUD, calculated using predictive margins in logistic regression models. We used the population of 2011 as the reference population to account for changes in the sex and age distribution.

To account for non-participation in both survey years, we used both weights and multiple imputation. In 2000, we used post-stratification weights to account for varying sampling probabilities and unit non-response (i.e. non-participation of individuals). These post-stratification weights were calibrated by Statistics Finland based on register information on age, gender, area and language (Lundqvist and Mäki-Opas, 2016). In 2011, we used inverse probability weights created with a model which included age, sex, education, self-reported work ability, mother tongue, self-rated health, social participation and the interactions terms of age, sex and education (see Lundqvist and Mäki-Opas, 2016 for details).

Secondly, we used multiple imputation of both exposure and outcome variables. Multiple imputation is a simulation-based procedure that replaces each missing value with a m >1 set of plausible values. This creates m complete datasets that are pooled to obtain a combined final estimate that incorporates both the variability of the data as well as the uncertainty about the missing values (Harel, et al., 2017). The imputation model should include the variables in the analysis model (including the outcome), as well as auxiliary variables that are predictive of the outcome and the missingness.

We exploited the richness of the Health 2000 dataset and the possibility to obtain additional information by linking the data on hospitalizations from the Finnish Hospital Discharge Register (HILMO) using personal identification codes assigned to all permanent residents in

Finland (Härkänen, et al., 2016). Thus, we used 28 variables on sociodemographic characteristics, mental and physical health, use of health services, health behaviours and hospital admissions for mental disorders until 2000 (for year 2000 analyses) and until 2011 (for year 2011 analyses). The full list of variables can be found in the Supplementary Appendix of the Sub-study II.

Multiple imputation was performed using multivariate imputation by chained equations (mice), which does not assume a multi-normal distribution and thus can be used for categorical and continuous variables (van Buuren, 2018). The multiple imputation was conducted separately in groups defined by gender and age (in three groups 30-54, 55-74 and 75+), where 24 imputed datasets were created using the *mice* package in R (van Buuren and Groothuis-Oudshoorn, 2011). Each dataset was analysed separately using the baseline sampling design and the results were combined using the *mi estimate* command in Stata SE/14.

Sociodemographic characteristics in each survey were compared by bivariable analyses using a chi square test. We used logistic regression models to examine the unadjusted and adjusted (to age, sex, marital status and educational level) associations between exposure and outcome variables.

In addition, we examined the possibility of selection bias (participants vs non-participants) by comparing the prevalence of AUD among respondents who participated both in 2000 and 2011 and those who did not participate in 2011 and also the rates of lifetime hospitalizations due to AUD in 2000 and 2011 (based on register-linked data). We also examined re-test bias by comparing the prevalence of AUD among those who were 30-41 in 2000 with the new cohort of participants 30 to 41 years old in 2011.

For brevity, we report only multiply imputed results. Weight-based results can be found in the published article.

Sub-study III. We modelled the time-to-event data using shared frailty Cox proportional hazard models. A shared frailty is a random effects model where the random effect is shared by all subjects within the cluster (Austin, 2017), in this case, the survey round. Participants were right-censored due to end-of-follow up (December 2016) or death due to a non-alcohol-attributable cause. We used attained age as the timescale (Korn, et al., 1997). Regression estimates are hazard ratios with 95% confidence intervals.

We tested the proportional hazard assumption for individual covariates in the final models by visual inspection of plotted scaled Schoenfeld residuals versus time and also testing the null

hypothesis of zero slope for individual covariates and globally (Harrell, 2015). In some of the models, the alcohol use variable did not fulfil the proportional hazards assumption, which means that the effect of alcohol use on the outcome was not constant over the follow-up time. We therefore modelled it as an age-varying covariate by splitting the analysis time in three intervals (at attained ages 55 and 70, based on visual inspection of the residuals) and fit a Cox proportional hazards model stratified for these time intervals (Zhang, et al., 2018).

We examined the linearity of the relationship between alcohol biomarkers and alcohol-attributable mortality by visual inspection of plotted martingale residuals (Therneau and Grambsch, 2000). None of the biomarkers showed a linear relationship. Further, we used a likelihood ratio test to compare a linear model with a model using a penalised smoothing spline to allow a non-linear relationship of the biomarker and the outcome (Ramsay, et al., 1997). GGT was the only significant non-linear relationship and was modelled using splines. CDT, AST and ALT were modelled as a linear relationship.

The analytical strategy consisted of evaluating first whether alcohol biomarkers provided additional information to self-reported alcohol use. We tested this by examining whether biomarkers were associated with the outcome and improved the predictive ability of the model. We examined the association between GGT and alcohol-attributable mortality by extracting the predicted values and plotting the values of GGT against the log hazard. For CDT, AST and ALT, we report the hazard ratios in model 4 (see below). The predictive ability was measured using the concordance statistic (C-index) (Harrell, 2015). The C-index denotes the strength of the rank correlation between predicted probability and actual response. A value of 0.5 indicates random prediction and a value of 1 indicates perfect prediction (Harrell, 2015). We compared the C-index in models adjusted for self-reported alcohol use and/or alcohol biomarkers and computed the difference in the C-index and tested the equality between the concordance values (Therneau and Atkinson, 2019).

We further used the change-in-estimate method to test whether alcohol biomarkers explained the association between SES and alcohol-attributable mortality (Baron and Kenny, 1986, MacKinnon, et al., 2000). The change-in-estimate method is a simple mediation analysis that quantifies the change in estimate (i.e. the hazard ratio of the lowest versus highest income and education group) after controlling for confounders (model 1 and 2) and self-reported alcohol use and/or alcohol biomarkers (models 3 to 5). Model 1 was adjusted for age (as timescale), sex and survey round (as shared frailty). Model 2 was additionally adjusted for smoking, body mass index, poor self-reported health and baseline health conditions. Model 3

was model 2 plus self-reported alcohol use. Model 4 was model 2 plus self-reported alcohol use and alcohol biomarkers. Model 5 was model 2 plus alcohol biomarkers.

If differential biases in the measurement of alcohol exposure explain the alcohol paradox, we expect that controlling for alcohol biomarkers in models 4 and 5 would attenuate the hazard ratio (of the lowest versus highest income and educational group) towards 1. We used model 2 as the reference model and calculated the percent change (% attenuation) in the β coefficient as follows (Stringhini, et al., 2017):

$$(2)\ Percent\ change\ = \left(\frac{\beta\ model\ 2\ -\ \beta\ models\ 3,4\ or\ 5}{\beta\ model\ 2}\right) * 100$$

Sub-study IV. We modelled the time-to-event data using additive hazard models. Additive hazard models have two advantages over Cox proportional hazard models: (i) the effects of covariates are allowed to vary freely over time and are not assumed constant as in Cox proportional hazard models, and (ii) allow a direct estimation of additive interactions, which have been suggested to be more relevant for public health and clinical decision-making, as they represent directly the risk differences and contribute to identify subgroups who would benefit from public health interventions (Greenland, et al., 2008, Rod, et al., 2012, VanderWeele and Knol, 2014). We considered a joint effect (also known as supra-additive effects) as a deviation from the additivity of the absolute effects, meaning that the combined effects of two variables are larger than the sum of their individual effects (Rod, et al., 2012).

We used a semi-parametric version of Aalen additive hazard models which allows to partition the effects of covariates that depend on time to those effects that are constant (Aalen and Scheike, 2005). In this model, the hazard for the outcome (i.e. alcohol-attributable mortality) for person *i* and age *t* is modelled as a linear function of the explanatory variables plus an unspecified baseline hazard. The timescale was attained age.

As a first step, we examined the existence of income-alcohol joint effects to confirm the findings from previous literature and assessed interactions between income and behavioural risk factors (income-smoking and income-BMI) and between alcohol and behavioural risk factors (alcohol-smoking and alcohol-BMI). We fitted a model,

$$(3)\ \lambda_i\ (t)\ =\ \lambda_0\ +\ \alpha_1 S_i + \alpha_2 M_i\ + \alpha_3 (S\ x\ M)_i\ +\ \beta(t) L_i$$

where S is income, M is the mediator for person i; α_1 and α_2 are the separate additive effects; α_3 is the coefficient of interest that captures the additive interaction between α_1 and α_2, and L_i are the potential confounders (i.e. sex, age, survey round and marital status). We fitted five models to assess the exposure-mediator and mediator-mediator joint effects outlined above.

The effect estimate is a hazard difference, interpreted as the number of additional alcohol-attributable deaths per 10,000 person years at risk in the specific exposure category (e.g. lowest income quintile) compared to a reference category (e.g. highest income quintile). To simplify presentation, we compared the lowest versus highest income quintile and the highest category of the mediator (high alcohol intake, current smoker and BMI ≥30) compared to the reference category (never or former drinker, never smoker and BMI between 18 and 25 kg/mt^2).

After identifying the existence of joint effects, we quantified the extent to which behavioural risk factors explained the alcohol harm paradox. The change-in-estimate method used in Sub-study III allows to estimate the change in the direct effect (i.e. of socioeconomic status on alcohol-attributable mortality). In Sub-study IV, we used causal mediation analyses that allows us to decompose the total effect of income (i.e. lowest vs highest income quintile) on alcohol mortality.

Causal mediation analysis is based on the potential outcomes framework (Robins, et al., 2000, VanderWeele and Vansteelandt, 2014). The approach creates a pseudo-population in which the exposure is no longer associated with observed confounders L_i (i.e. no residual confounding by L_i). We used inverse probability to treatment weights (IPTW) to assign to each person i a weight w_i equal to the inverse of the probability of receiving his/her own exposure. A model is fitted including the exposure but using the pseudo-population constructed by IPTW, known as a Marginal Structural Model (MSM) (Robins, et al., 2000).

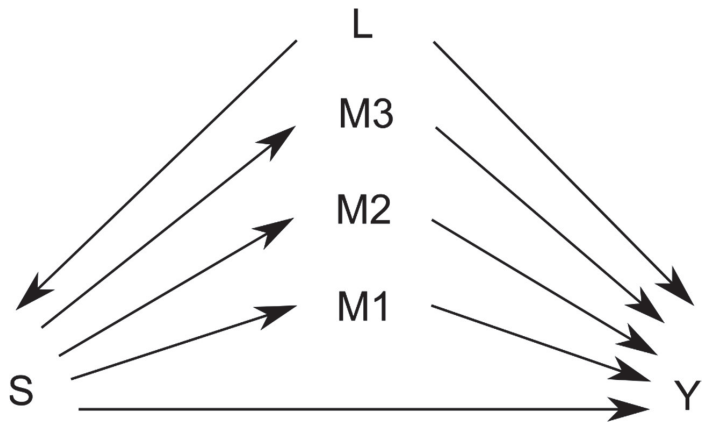
We carried out a three-way decomposition that allows a decomposition of the total effect of income into three components (Lange and Hansen, 2011, VanderWeele, 2013): (i) a pure direct effect (PDE) of income on alcohol-attributable mortality, (ii) a pure indirect effect (PIE) through each mediator (differential exposure) and (iii) a mediated interactive effect (INTmed) between the mediators and income (differential vulnerability). The proportion mediated by a given mediator is the sum of pathways (ii) and (iii). The interpretation of the proportion mediated can be best understood in terms of a hypothetical intervention that would bring the levels of the mediator in the lowest income quintile to the level of the highest income quintile. For example, the proportion mediated by smoking can be interpreted as the effect on alcohol-attributable mortality of bringing the prevalence of smoking from the lowest income quintile to the highest

income quintile (in data for Sub-Study IV, 27.1% vs 24.5% respectively) (Diderichsen, et al., 2018).

The total effect, which is equivalent to a minimally-adjusted model, is the sum of pathways (i), (ii) and (iii). For the practical implementation, we used the method developed by Lange for additive hazard models. A more detailed description of the method and the statistical code used can be found in the Supplementary Appendix of Sub-study IV.

The causal interpretation of the effects rests on four fairly strong assumptions: (a) no exposure-outcome confounding, (b) no mediator-outcome confounding, (c) no exposure-mediator confounding, and (d) no mediator-outcome confounder that is affected by the exposure. Assumptions (a) and (c) are common in observational studies for total effects. Assumption (b) is specific for causal mediation analysis, as it is needed for the analysis of direct and indirect effects (VanderWeele, 2016).

Figure 4. Directed acyclic graph of the causal relationship between income (S), behavioural risk factors (M) and alcohol-attributable mortality (Y)



M1, M2 and M3 represent the mediators (alcohol use, smoking and Body Mass Index). For clarity, arrows between L and M1, M2 and M3 are not drawn. L represents a vector of confounders.

We tested for time invariant effects using a resampling approach (Scheike and Martinussen, 2006). Sex, marital status and alcohol use were time-variant, as a result, we allowed sex and marital status to vary freely over time. To obtain a coefficient, we modelled alcohol use as having time-invariant (constant) effects and ran sensitivity analyses for four age subgroups, where the time-invariant assumption was met (see Supplementary Appendix in Sub-study IV for details).

Additional sensitivity analyses. Specific sensitivity analyses were carried out in Sub-study III and IV and are described in the respective published articles. A more general concern is how to handle non-drinkers, given alcohol is a necessary cause of alcohol-attributable mortality. On the one hand, non-drinkers represent a large segment of the study population and, for reasons discussed in section 2.1.4, might not be correctly identified with questionnaires used in population health surveys, which cover a specific period of time. Given this, the drinking/non-drinking status is a fluctuating state and not a permanent characteristic of the respondents. In other words, the abstainer category includes drinkers who have been misclassified. A second argument is related to the counterfactuals discussed above. A hypothetical target trial (i.e. a hypothetical randomized controlled trial that would answer our research question) would ideally consist of randomly assigning individuals to different income status, without manipulating alcohol exposure. Hence, the target trial would include all kinds of drinkers, including abstainers. Likewise, the hypothetical intervention described above to understand the proportion mediated implies hypothetical changes in the volume of alcohol use, which can include abstainers becoming drinkers.

On the other hand, there is the concern that including abstainers could bias the estimates of socioeconomic inequalities among those who drink, given abstaining is more prevalent in lower socioeconomic groups and might affect the estimates in Sub-studies I, III and IV. To account for this potential bias, additional sensitivity analyses were carried out excluding abstainers.

5 Results

5.1 SOCIOECONOMIC DIFFERENCES IN ALCOHOL USE (SUB-STUDY I)

The distribution of each of the alcohol use indicators by educational quintiles can be found in Table 9. In Finland, there was a gradient of higher abstinence and heavy episodic drinking among lower socioeconomic groups. In Chile, abstinence was higher among lower socioeconomic groups, while no clear pattern was observed for the other alcohol use indicators. Sensitivity analysis excluding 12-month abstainers in Finland showed that mean grams of alcohol use were higher in the lower SES group compared to higher SES groups. Prevalence of heavy volume drinking and heavy episodic drinking increased in all groups, but proportionally more in the lowest educational quintile. Similarly, in Chile, all indicators of alcohol use increased, but proportionally more in the lower socioeconomic groups.

The overall socioeconomic differences in alcohol abstinence were -0.25 in Finland (95% CI -0.33; -0.16) and -0.19 in Chile (95% CI -0.23; -0.16) (Figure 5). This indicates that the prevalence of abstinence is higher in lower socioeconomic groups. In Finland, alcohol abstinence was higher among women of lower SES in both 25-44 and 45-64 age groups as well as in men aged 45-64 years. In Chile, lower SES was associated with higher alcohol abstinence in women in both age groups. Among men in the 45-64 age group, the confidence intervals were mostly compatible with higher prevalence of abstinence in those with lower SES, but we were unable to find evidence against the null hypothesis (i.e. concentration index = 0).

Socioeconomic differences in weekly grams of alcohol used were not as clear. In Finland, we did not find evidence of differences in overall weekly grams of alcohol used by SES. Men in the 25-44 age group of lower SES were more likely to have a higher weekly alcohol use; we observed the inverse among men and women in the 45-64 age group, where people of lower SES were less likely to report higher weekly alcohol use. The effect sizes were in general very small. In Chile, we observed overall higher levels of weekly alcohol use among higher socioeconomic groups. This was primarily driven by higher weekly alcohol use among women in the 45-64 age group.

Table 9. Alcohol indicators by educational quintiles in Finland and Chile

	Educational quintile				
Finland	Lowest	2nd	3rd	4th	Highest
n	2037	1947	2547	1791	1511
Abstinence, %	17.7	10	10.1	8.2	7.1
Mean grams of pure alcohol per week (SD)	69.0 (116.6)	76.9 (109.5)	68.7 (101.6)	67.2 (96.3)	69.5 (93.4)
Heavy volume drinking, %	9.4	10.8	9.5	8.6	9.9
Heavy episodic drinking, %	33	34.1	29.1	25	24.5
Excluding 12-month abstainers					
Mean grams of pure alcohol per week (SD)	85.2 (124.4)	86.5 (112.5)	77.0 (104.6)	74.1 (98.6)	75.6 (95.0)
Heavy volume drinking, %	11.7	12.1	10.7	9.5	10.8
Heavy episodic drinking, %	40.1	37.8	32.2	27.2	26.3
Chile	Lowest	2nd	3rd	4th	Highest
n	700	875	1154	107	636
Abstinence, %	40.1	26.8	25	23.2	15.8
Mean grams of pure alcohol per week (SD)	21.1 (71.5)	28.0 (70.5)	26.7 (91.9)	38.3 (66.2)	34.1 (127.6)
Heavy volume drinking, %	2.5	3.3	2.1	6.1	2.2
Heavy episodic drinking, %	13.5	17.1	13.3	14.1	11.1
Excluding 12-month abstainers					
Mean grams of pure alcohol per week (SD)	35.3 (89.6)	38.2 (80.0)	35.6 (104.6)	49.9 (71.7)	40.5 (138.2)
Heavy volume drinking, %	4.1	4.6	2.8	7.9	2.6
Heavy episodic drinking, %	22.5	23.4	17.7	18.4	13.2

Heavy volume drinking was defined as alcohol drinking higher than 30 grs in men and 20 gr in women per day. Heavy episodic drinking was defined as participants drinking more than 6 drinks per occasion once a month or more often in Finland and 5 drinks in Chile.

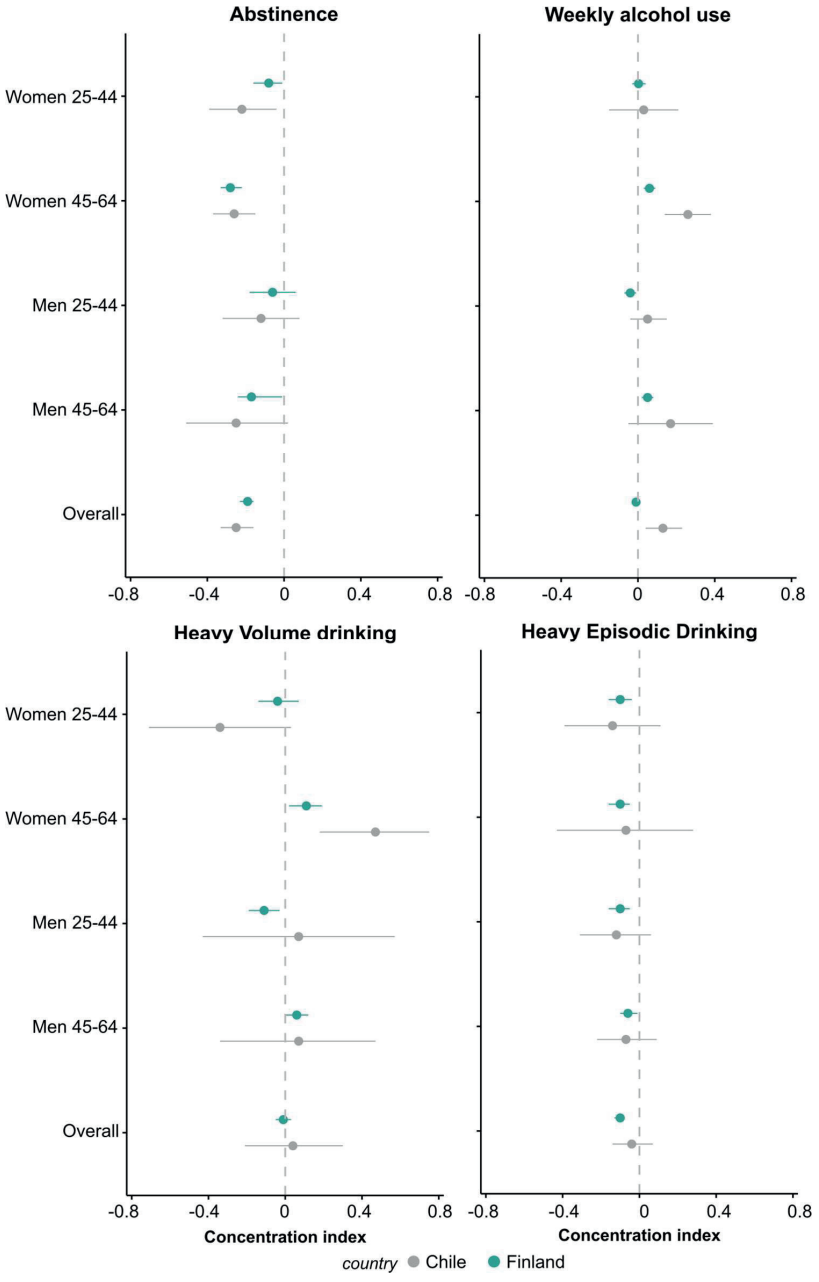
The analysis of socioeconomic differences in heavy volume drinking showed similar patterns as weekly grams of alcohol used. The overall socioeconomic differences in heavy volume drinking were -0.01 in Finland (95% CI -0.05; 0.03) and 0.04 in Chile (95% CI -0.21; 0.3). In Finland, we found evidence of higher heavy volume drinking among lower socioeconomic groups in men aged 25-44 years and among higher socioeconomic groups in women aged 45-64. In Chile, heavy volume drinking was much higher among women aged 45-64 of higher SES

(concentration index 0.47, 95% CI 0.18; 0.75). We did not find evidence of socioeconomic differences in the other groups.

Heavy episodic drinking was more prevalent in lower socioeconomic groups in Finland. The overall socioeconomic differences in Finland were -0.10 (95% CI -0.13; -0.08) and in Chile -0.04 (95% CI -0.14; 0.07). In Finland, all gender and age groups showed higher HED among lower socioeconomic groups. These differences were overall relatively small. In Chile, we did not find clear evidence of socioeconomic differences in HED any gender or age group as in Finland.

Analyses excluding 12-month abstainers (Tables A1-3 in Appendix) resulted in very similar estimates in Finland. In Chile, for weekly grams of alcohol used, results excluding 12-month abstainers were very similar to the ones in the whole population. For heavy volume drinking, the only marked change in the concentration index was for men aged 25-44, were it changed from 0.07 (95% CI -0.43; 0.57) to -0.27 (95% CI -0.48; -0.07). For heavy episodic drinking, all concentration indices became more negative and statistically significant. All in all, excluding 12-month abstainers did not produce substantially different results than the main analyses.

Figure 5. Concentration index of alcohol use indicators in Finland and Chile



5.2 PREVALENCE AND SOCIOECONOMIC DIFFERENCES IN ALCOHOL USE DISORDERS (SUB-STUDY II)

The estimated prevalence of 12-month AUD decreased from 4.6% (95% CI 4.0-5.1) in 2000 to 2.0% in 2011 (95% CI 1.6; 2.4). Twelve-month prevalence among men was 7.5% in 2000 and 3.2% in 2011, while the prevalence among women was 2.0% in 2000 and 0.9% in 2011. The prevalence ratio between men and women remained relatively stable (3.8 in 2000 and 3.6 in 2011).

AUD were more prevalent in the younger age groups (30-44 and 44-54) in both 2000 and 2011. We observed a reduction in 12-month prevalence across all age groups, for example, the prevalence of AUD among participants 30 to 44 years old decreased from 6.1% in 2000 (95% CI 5.0; 7.2) to 2.7% in 2011 (95% CI 1.8; 3.6) (Table 10).

The prevalence of 12-month AUD was highest among those with intermediate education (i.e. high school or completed vocational school) both in 2000 and 2011. We observed a reduction of similar magnitude in the prevalence of AUD in all educational groups. For example, prevalence of 12-month AUD among those with basic education decreased from 3.7% in 2000 to 2.0% in 2011. Participants who were unmarried, widowed or divorced showed a higher prevalence of 12-month AUD in 2000 and 2011, compared to married or cohabiting individuals (Table 10). There was a reduction in the prevalence of AUD in both marital status categories between 2000 and 2011.

In logistic regression models, women in 2011 had 73% lower odds of 12-month AUD than men (OR 0.27, 95% CI 0.16; 0.45), people aged 65-74 and 74+ had lower odds of AUD than the 30-44 age group and those unmarried, widowed or divorced had 2.7 times higher odds of AUD than those married or cohabiting (OR 2.7, 95% CI 1.7; 4.1). Regarding educational differences, we did not find evidence that those with intermediate or high education had different odds than the ones with basic education, as the confidence intervals were compatible with a wide range of potential associations.

Table 10. Prevalence of 12-month AUD in 2000 and 2011 and odds ratios of fully adjusted logistic regression models

	2000			2011		
	n	Prevalence (95% CI)	AOR (95% CI)	n	Prevalence (95% CI)	AOR (95% CI)
Overall	255	4.6 (4.0-5.1)	-	76	2.0 (1.6–2.4)	-
Age						
30-44	131	6.1 (5.0-7.2)	1	26	2.7 (1.8–3.6)	1
45-54	71	5.0 (3.9-6.1)	0.84 (0.62; 1.14)	24	2.3 (1.4–3.2)	0.79 (0.48–1.31)
55-64	44	4.3 (3.1-5.5)	0.75 (0.52; 1.06)	17	1.9 (1.1–2.7)	0.61 (0.33–1.12)
65-74	7	1.9 (1.1-2.7)	0.32 (0.20; 0.69)	7	1.1 (0.6–1.6)	0.39 (0.18–0.87)
75+	2	2.0 (0.9-3.0)	0.37 (0.20; 0.69)	2	0.8 (0.1–1.5)	0.22 (0.07–0.71)
Sex						
Male	206	7.5 (6.6-8.5)	1	57	3.2 (2.5–4.0)	1
Female	49	2.0 (1.5-2.4)	0.25 (0.19-0.34)	19	0.9 (0.5–1.3)	0.27 (0.16–0.45)
Educational level						
Basic	70	3.7 (2.9-4.4)	1	18	2.0 (1.2–2.7)	1
Intermediate	105	5.5 (4.5-6.6)	1.10 (0.81; 1.48)	31	2.4 (1.7–3.1)	0.79 (0.45–1.36)
High	80	4.7 (3.7-5.7)	1.10 (0.79; 1.54)	27	1.6 (1.1–2.2)	0.63 (0.35–1.15)
Marital status						
Married or cohabiting	160	4.0 (3.4-4.6)	1	35	1.5 (1.1–1.9)	1
Unmarried, widowed or divorced	95	5.8 (4.7-6.8)	1.83 (1.4; 2.37)	41	3.2 (2.2–4.2)	2.65 (1.72–4.09)

Results are from multiple imputation. AOR are adjusted odds ratios from logistic regression models adjusted to sex, age, educational level and marital status.

The estimated lifetime prevalence of AUD also decreased from 10.8% in 2000 to 7.5% in 2011. The sociodemographic correlates were similar: there was a higher prevalence among men, younger age groups, participants with intermediate education and unmarried, widowed and divorced.

To assess selection bias, we compared the prevalence of register-linked lifetime hospitalizations for alcohol dependence among participants and non-participants (Table 11). Non-participants had a higher lifetime hospitalization for alcohol dependence compared to

participants in both surveys (3.2% vs 0.9% in 2000 and 4.1% vs 1.8% in 2011). Those who participated in 2000 but not in 2011 also had higher hospitalization rates for alcohol dependence than participants in both surveys (2.8% vs 0.9% in 2000 and 3.9% vs 1.8% in 2011). This indicates that individuals with alcohol dependence were less likely to participate in both 2000 and 2011.

Regarding information bias, the estimated lifetime prevalence of AUD in people who participated in both survey waves decreased from 2000 to 2011 (9.6% in 2000 versus 6.0% in 2011), suggesting the presence of information bias (i.e. lifetime prevalence should not decrease) (Table 11). As expected, lifetime prevalence of hospitalization due to alcohol dependence increased between 2000 and 2011 among CIDI participants (as incident cases accumulate). However, participants aged 30-41 years in 2011, for whom the CIDI was not performed in 2000 (i.e. were not re-tested), reported a lower prevalence of 12-month and lifetime AUD than participants aged 30-41 years in 2000. Lifetime hospitalizations due to alcohol dependence in these two groups remained stable at 0.8%.

Table 11. Prevalence of 12-month, lifetime AUD and lifetime hospitalization for alcohol dependence for sub-study groups

	12-month AUD, %		Lifetime AUD, %		Lifetime hospitalization for alcohol dependence, %	
Study subgroup	**2000**	**2011**	**2000**	**2011**	**2000**	**2011**
Nonparticipants 30+ in 2000					3.2	-
Nonparticipants 30+ in 2011					-	4.1
CIDI participants in both 2000 and 2011	3.9	1.5	9.6	6.0	0.9	1.8
CIDI participants in 2000 and not 2011	4.2		10.6		2.8	3.9
CIDI participants age group 30-41 in 2000	5.8		13.5		0.8	
CIDI participants age group 30-41 in 2011		2.4		8.7		0.8

Prevalence estimates are crude (i.e. without weights or multiple imputation). Lifetime hospitalization was calculated during the lifetime until survey year (2000 and 2011, respectively)

5.3 SOCIOECONOMIC DIFFERENCES IN ALCOHOL MORTALITY (SUB-STUDY III-IV)

In Sub-studies III and IV, we examined the socioeconomic differences in alcohol mortality. In the Sub-study III dataset, there were 828 alcohol-attributable deaths in total, over a follow-up period of 1,056,844 person-years. Participants in the lowest income quintile had a much higher alcohol-attributable mortality than those in the highest income quintile (death rate 11.8 versus 6.8 per 10,000 person-years, respectively). Educational differences in alcohol mortality followed a similar pattern: participants with basic education had a death rate of 9.1 compared to 4.8 per 10,000 person-years in those with high education.

In minimally-adjusted models (i.e. adjusted for age, sex and survey round), participants in the lowest income quintile had 2.1 times higher alcohol mortality than those in the highest income quintile (HR 2.1, 95% CI 1.7; 2.5) (Figure 6). Participants with basic education had 67% higher risk of alcohol mortality compared with those with high education (HR 1.67, 95% CI 1.3; 2.2). Comparing all income quintiles, we observed that the lowest income group had clearly higher alcohol mortality, while the second income quintile had confidence intervals mostly compatible with higher alcohol-attributable mortality, but we were unable to find evidence against the null hypothesis. The third and fourth income quintiles showed levels of alcohol mortality similar to that in the highest income quintile. Additional sensitivity analyses excluding never and former drinkers (Figure 6, b) resulted in an increase in hazard ratios for all income quintiles, which was proportionally larger for the lowest income quintile.

Figure 6. Hazard ratio of income quintiles (using the highest income quintile as a reference) for alcohol-attributable mortality in the whole population (a) and excluding never and former drinkers (b)

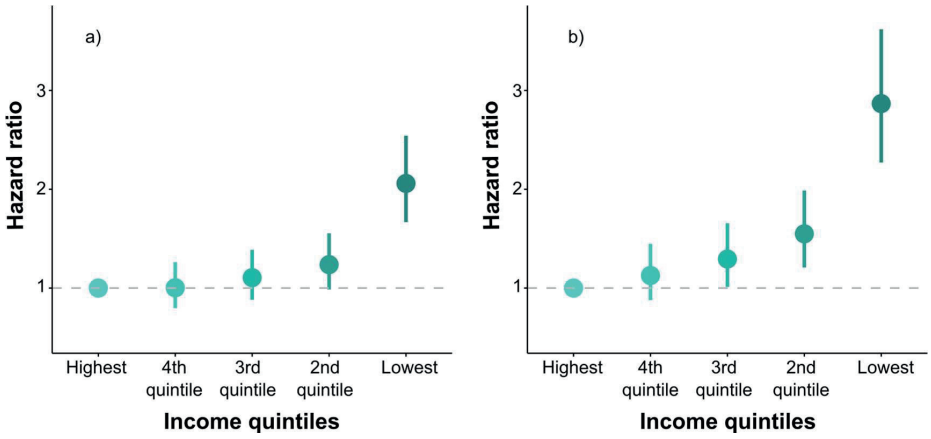


Table 12 shows the specific causes for alcohol-attributable deaths. In 30% of alcohol-attributable deaths, the underlying cause of death was attributable to alcohol, while in 14.7% both the underlying and the contributory cause of death were alcohol-attributable. In 55.3% of cases, the contributory cause of death alone was alcohol-attributable. The immediate cause of death was attributable to alcohol in 32 cases, never as the only alcohol-attributable cause. The most common underlying cause of alcohol-attributable death was alcoholic liver disease (21.4%), followed by alcohol intoxication (8%) and mental and behavioural disorders due to alcohol (6.5%). The most common contributory causes of death were mental and behavioural disorders due to alcohol (50.1%) and alcoholic liver disease (14.7%).

Table 12. The underlying, contributory and immediate causes of death for the alcohol-attributable deaths (n=828) in the pooled data from eight Finnish cohort studies

Wholly attributable conditions	**ICD-10 code**	**Underlying**	**Contributory**	**Immediate**
Alcohol-induced pseudo-Cushing's syndrome	E244	0	0	0
Mental and behavioural disorders due to use of alcohol	F10	6.5% (54)	50.1% (415)	0.4% (3)
Degeneration of nervous system due to alcohol	G312	0.8% (7)	1.4% (12)	0
Epileptic seizures related to alcohol	G4051	0.7% (6)	0.4% (3)	0
Alcoholic polyneuropathy	G621	0	0.1% (1)	0
Alcoholic myopathy	G721	0	0	0
Alcoholic cardiomyopathy	I426	2.5% (21)	1.4% (12)	0.2% (2)
Alcoholic gastritis	K292	0.1% (1)	0	0
Alcoholic liver disease	K70	21.4% (177)	14.7% (122)	1.7% (14)
Alcohol-induced acute pancreatitis	K852	1.3% (11)	0.1% (1)	0.4% (3)
Alcohol-induced chronic pancreatitis	K860	0.2% (2)	1.2% (10)	0
Maternal and foetal damage from alcohol	O354	0	0	0
Finding of alcohol in blood	R780	0	0	0
Toxic effect of alcohol	T51	0	0	0
Accidental poisoning by and exposure to alcohol	X45	8% (66)	0.1% (1)	0
Intentional self-poisoning by and exposure to alcohol	X65	0.8% (7)	0.4% (3)	1.2% (10)
Poisoning by and exposure to alcohol, undetermined intent	Y15	2.2% (18)	0	0
Evidence of alcohol involvement determined by blood alcohol level or level of intoxication	Y90, Y91	0	0	0
Alcohol-attributable causes combined		44.7% (370)	70.0% (580)	5.5% (32)
Cause not alcohol-attributable		55.3% (458)	11.2% (93)	25.5% (211)
Not recorded		0	18.7% (155)	70.7% (585)
Total[1]		100 (828)	100 (828)	100 28)

Cause-specific alcohol-attributable deaths are from the dataset in Sub-study III (total number of deaths = 828). 1. The sum of alcohol deaths is higher than 828 because a person can have both an underlying, contributory, and/or immediate alcohol-attributable code.

5.4 ALCOHOL HARM PARADOX (SUB-STUDY III-IV)

In Sub-studies III and IV, we were able to compare socioeconomic differences in alcohol use and mortality in the same dataset. We used the same indicators as in Sub-study I to provide greater comparability (Table 13). We observed a clear gradient for alcohol abstinence, where lower socioeconomic groups had higher rates of alcohol abstinence than those with higher SES. For example, 56.9% of participants in the lowest income quintile reported being never or former drinkers compared to 26.2% in the highest income quintile.

Weekly volume of alcohol use also showed a clear socioeconomic gradient. Participants in the lowest income quintile consumed on average 40 grams of alcohol per week (e.g. equivalent to four cans of beer) versus 75.5 grams of alcohol per week in the highest income quintile. The proportion of heavy volume drinkers (those with high and very high intake) also varied by socioeconomic status in the same direction, but in this case the gradient was less clear. The lowest, second and third income quintile had lower rates of heavy volume drinkers than the fourth and highest income quintile (e.g. 3.7% in the lowest quintile versus 7% in the highest income quintile). Heavy episodic drinking was higher among higher income groups, with a clear gradient.

Similar patterns were observed for education. Participants with basic education showed higher levels of abstinence (51% vs 26.3%), lower weekly grams of alcohol used (43.1 vs 67.8 grams/week) and less prevalent heavy volume drinking (3.6% vs 5.7%) compared to those with high education. HED was also higher among those with higher education (22.4% among those with high education vs 15.9% among those with basic education). Additional sensitivity analyses excluding never and former drinkers, resulted in a reduction of the observed gradients for weekly alcohol use, heavy volume drinking and HED for both income and education.

Table 13. Alcohol use indicators by income quintiles in eight pooled cohorts in Finland

	Income quintile				
	Lowest	**2nd**	**3rd**	**4th**	**Highest**
n	10530	10640	10123	10663	10208
Abstinence, %	56.9	46.5	38.8	33.3	26.2
Mean grams of pure alcohol per week (SD)	40.0 (100.4)	45.5 (88.9)	52.7 (92.3)	60.2 (95.4)	75.4 (111.1)
Heavy volume drinking, %	3.7	3.6	4.1	4.8	7.0
Heavy episodic drinking, %[1]	17.6	17.5	17.9	20	22.5
Excluding never and former drinkers					
Mean grams of pure alcohol per week (SD)	92.6 (135.9)	85.0 (106.8)	86.2 (105.1)	90.3 (104.5)	102.2 (118.3)
Heavy volume drinking, %	8.6	6.7	6.7	7.3	9.5
Heavy episodic drinking, %[1]	26.3	24.2	23.4	24.9	26.2

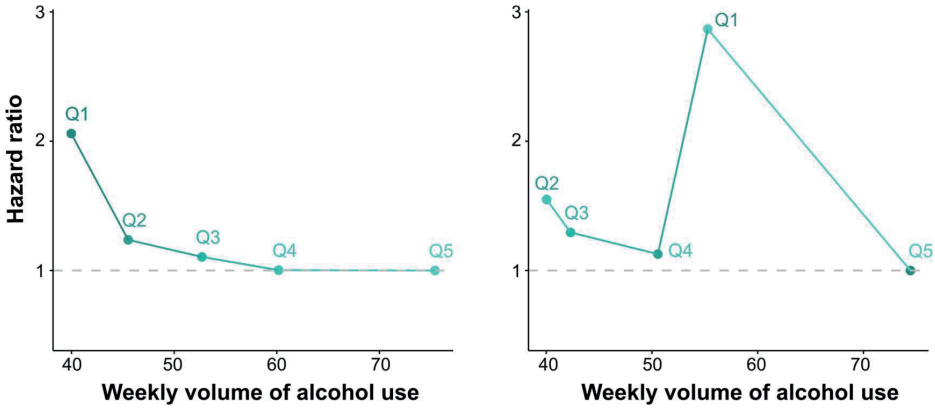
	Educational levels		
	Basic	**Intermediate**	**High**
n	24752	19395	9971
Abstinence, %	51	35.8	26.3
Mean grams of pure alcohol per week (SD)	43.1 (94.4)	60.8 (101.0)	67.8 (98.8)
Heavy volume drinking, %	3.6	5.3	5.7
Heavy episodic drinking, %[1]	15.9	19.7	22.4
Excluding never and former drinkers			
Mean grams of pure alcohol per week (SD)	88.1 (119.4)	94.7 (112.5)	92.1 (105.0)
Heavy volume drinking, %	7.3	8.2	7.7
Heavy episodic drinking, %[1]	23.1	25.2	26.4

1. Heavy episodic drinking was available from FINRISK 1987-2007 and Health 2000. Heavy volume drinking was defined as alcohol drinking equal or higher than 252 grs in men and 168 gr in women per week. Heavy episodic drinking was defined as participants drinking more than 5 drinks per occasion once a month or more often.

All in all, lower socioeconomic groups had higher abstinence, lower weekly alcohol use and heavy volume drinking levels, but had a much higher alcohol-attributable mortality. This indicates the existence of the alcohol harm paradox in the Finnish population. Figure 7 shows the alcohol paradox visually, using volume of alcohol use. Excluding never and former drinkers (Figure 7, b) shows that differences in volume alcohol use between lowest and highest income

quintile tend to equalize, but differences in alcohol-related mortality become larger (as shown in section 5.3), illustrating the alcohol harm paradox as well.

Figure 7. Hazard ratios of alcohol-attributable mortality and weekly volume of alcohol use for each income quintile



Q1 Lowest income quintile, Q5 Highest income quintile

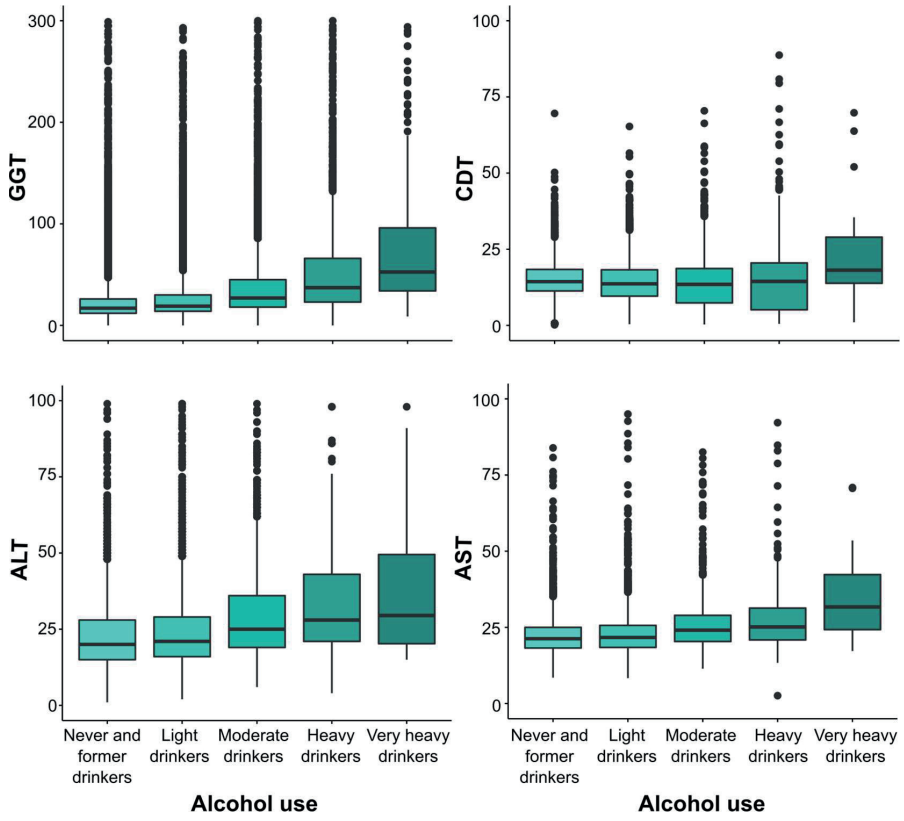
5.5 EXPLANATORY FACTORS FOR THE ALCOHOL HARM PARADOX (SUB-STUDY III-IV)

5.5.1 MEASUREMENT ERROR USING ALCOHOL BIOMARKERS

We observed alcohol-attributable deaths in all categories of volume alcohol drinking. Never and former drinkers experienced 147 alcohol-attributable deaths (death rate 3.3 per 10,000 person-years), while the light drinkers group experienced 189 alcohol-attributable deaths (death rate 4.6 per 10,000 person-years). In the case of alcohol biomarkers, we first examined whether alcohol biomarkers were associated with alcohol-attributable mortality and provided additional information to self-reported measures of alcohol use.

Figure 8 shows the distribution of biomarker levels by alcohol use category. GGT, ALT and AST showed a clear gradient of higher levels with higher self-reported alcohol use. In the case of CDT, there was a clear difference between the highest level of alcohol use compared to the other categories.

Figure 8. Box plots of biomarker levels (GGT, CDT, ALT and AST) against self-reported alcohol use categories



All alcohol biomarkers were associated with higher alcohol mortality in fully adjusted models (i.e. adjusted to age, sex, survey round, marital status, smoking, BMI, poor self-rated health and baseline health conditions). GGT showed a non-linear association where higher GGT levels were associated with higher alcohol mortality, resembling a saturated exponential curve. A 10-unit increase in CDT was associated with a 26% increased risk of alcohol mortality (HR 1.026, 95% CI 1.005; 1.05). A 10-unit increase in AST and ALT was associated with 3.3% and 4.4% increases in alcohol mortality risk, respectively (HR for AST 1.003, 95% CI 1.0008; 1.006 and HR for ALT 1.004, 95% CI 1.00; 1.01).

Secondly, we used the C-index to examine the changes in the predictive ability using biomarkers. Using alcohol biomarkers together with self-reported alcohol use improved the predictive ability for all biomarkers compared to using only self-reported alcohol use (Table 14). We also found that using GGT plus ALT alone improved the predictive ability compared to using only self-reported alcohol use, while evidence regarding the use of GGT, GGT plus CDT and GGT plus AST alone was inconclusive. Nonetheless, the change in the C-index when using together self-reported alcohol use, GGT plus ALT was greater than when using only GGT plus ALT, suggesting that even in this case, the use of self-reported alcohol use in conjunction with alcohol biomarkers provides additional information to that provided by biomarkers alone.

Table 14. Predictive ability using self-reported alcohol use and/or alcohol biomarkers

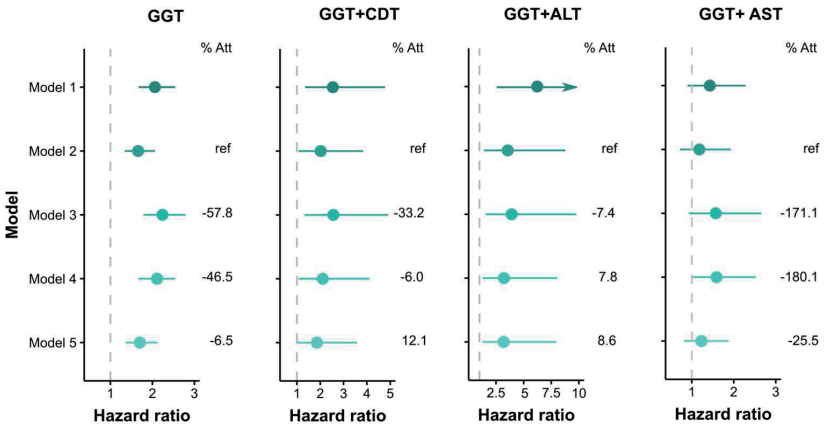
Adjusted model plus:[1]	C-index	C-index change
All cohorts		
Self-reported alcohol use	0.823	ref
Self-reported alcohol use + GGT	0.844	**0.021****
GGT	0.825	0.002
Subsample with CDT		
Self-reported alcohol use	0.841	ref
Self-reported alcohol use + GGT + CDT	0.864	**0.023****
GGT + CDT	0.856	0.015
Subsample with ALT		
Self-reported alcohol use	0.869	ref
Self-reported alcohol use + GGT + ALT	0.897	**0.028****
GGT + ALT	0.894	**0.025***
Subsample with AST		
Self-reported alcohol use	0.859	ref
Self-reported alcohol use + GGT + AST	0.871	**0.012****
GGT + AST	0.842	-0.017

C-index measures the model's predictive ability. Values range from 0.5 (random prediction) to 1 (perfect prediction). GGT gamma-glutamyl transferase, CDT carbohydrate-deficient transferrin, AST alanine aminotransferase, ALT aspartate aminotransferase. 1. Model adjusted for sex, age (as timescale), survey round, marital status, smoking status, body mass index, poor self-rated health, self-reported history of diabetes, myocardial infarction, stroke, emphysema and gallstones. C-index change refers to the difference between the C-index of model with alcohol use and biomarker or biomarker alone and the model with only self-reported alcohol use. Significant p-values are bolded * = p-value <0.05, ** = p-value < 0.01

Further, we examined the change in hazard ratios after adding covariates in nested models, comparing the lowest versus the highest income level (Figure 9). Hazard ratios attenuated after adjusting for marital status, smoking, body mass index, poor self-rated health and baseline health conditions (model 2). For example, in the full sample (GGT only models), the hazard ratio attenuated from 2.1 in model 1 to 1.7 in model 2.

Adjusting further for self-reported alcohol use (model 3) resulted in an increase in HRs in all models (attenuation percent ranged from -7.4% to -171.1%). Adjusting for both self-reported alcohol use and alcohol biomarkers (model 4) resulted in a reduction of 7.8% in the HR (GGT plus ALT models) or in an increase in HRs with the other biomarkers compared to model 2. Adjusting for the alcohol biomarker alone (model 5), resulted in a small reduction in the HRs in the case of GGT plus CDT and GGT plus ALT and an increase in HRs in GGT alone and GGT plus AST. In other words, the self-reported alcohol use variable is masking SES differences. Adjusting for both self-reported alcohol use and biomarkers also results in this kind of masking effect in three out of four models. Adjusting only for alcohol biomarkers results in a smaller masking effect and in an attenuation of the socioeconomic difference in two models. Nonetheless, this attenuation of the SES difference is relatively small (12.1% at most).

Figure 9. Hazard ratios of alcohol-attributable mortality for the lowest versus highest income level after adjusting for covariates



% Att Percent attenuation. GGT gamma-glutamyl transferase, CDT carbohydrate-deficient transferrin, ALT aspartate aminotransferase, AST alanine aminotransferase.

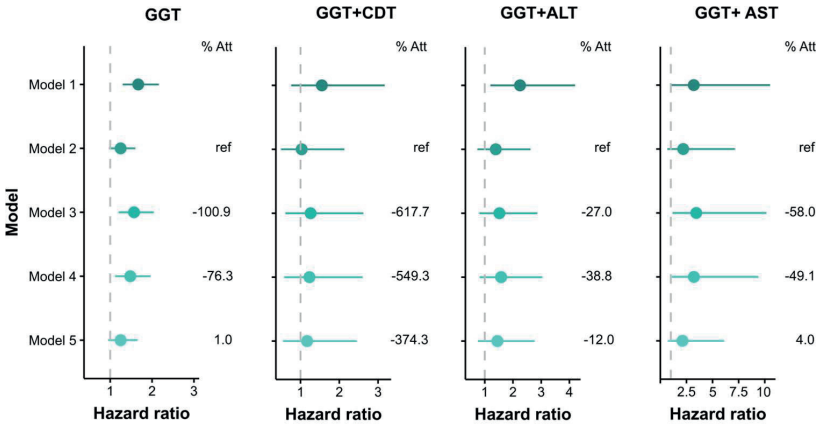
Percent attenuation = 100 x $(\beta_{Model\ 2} - \beta_{Model\ 3,4\ or\ 5})/\beta_{Model\ 2})$

Model 1: adjusted for sex, age and survey round. Model 2: model 1 plus marital status, smoking, BMI, poor self-rated health, and baseline health conditions. Model 3: model 2 plus self-reported alcohol use. Model 4: model 2 plus self-reported alcohol use and alcohol biomarker. Model 5: model 2 plus alcohol biomarker. Baseline health conditions include self-reported history of diabetes, myocardial infarction, stroke, emphysema and gallstones. GGT includes data from 52164 participants and 828 deaths, GGT+CDT analyses include 7240 participants and 100 deaths, GGT+ALT analyses include 7758 participants and 77 deaths, GGT+AST include 7043 participants and 131 deaths.

Analyses using educational levels (Figure 10) showed similar patterns. In all models, hazard ratios attenuated after adjusting additionally for marital status, smoking, body mass index, self-rated health and baseline health conditions (model 2). Adjusting further for self-reported alcohol use alone (model 3) or together with alcohol biomarkers (model 4) resulted in an increase in HRs for all biomarkers. Adjusting only for alcohol biomarkers resulted in an attenuation of 1% for the model with GGT and 4% in the model with GGT plus AST and resulted in an increase in the HR for the other two biomarkers.

All in all, then, whichever alcohol use measure or their combination is used (self-report, biomarker or both) to account for socioeconomic differences in exposure to alcohol use, socioeconomic differences in alcohol-related mortality remained wholly or largely unexplained.

Figure 10. Hazard ratios of alcohol-attributable mortality for basic versus high education after adjusting for covariates



% Att Percent attenuation. GGT gamma-glutamyl transferase, CDT carbohydrate-deficient transferrin, ALT aspartate aminotransferase, AST alanine aminotransferase.

Percent attenuation = 100 x $(\beta_{Model\ 2} - \beta_{Model\ 3,4\ or\ 5})/\beta_{Model\ 2}$)

Model 1: adjusted for sex, age and survey round. Model 2: model 1 plus marital status, smoking, BMI and baseline health conditions. Model 3: model 2 plus self-reported alcohol use. Model 4: model 2 plus self-reported alcohol use and alcohol biomarker. Model 5: model 2 plus alcohol biomarker. Baseline health conditions include poor self-rated health, self-reported history of diabetes, myocardial infarction, stroke, emphysema and gallstones. GGT includes data from 54118 participants and 858 deaths, GGT+CDT analyses include 7410 participants and 103 deaths, GGT+ALT analyses include 8028 participants and 81 deaths, GGT+AST include 7148 participants and 131 deaths.

5.5.2 JOINT EFFECTS OF SOCIOECONOMIC STATUS AND BEHAVIOURAL RISK FACTORS

In Sub-study IV, we first examined whether there were exposure-mediator joint effects (i.e. between income and the three mediators) and mediator-mediator joint effects (i.e. between the mediators) (Table 15). We observed the existence of joint effects between income and alcohol use and income and smoking. Participants in the lowest income quintile and the highest level of alcohol use had 46.8 additional alcohol-attributable deaths per 10,000 person years (95% CI 25.0; 68.6) due to the interaction. Participants in the lowest income quintile and who were current smokers had 11.4 extra deaths due to the interaction (95% 5.8; 17.0). We did not find evidence against the null hypothesis (i.e. no joint effect) for the joint effects between income and body mass index and mediator-mediator interactions, probably due to insufficient statistical power in the case of the alcohol use-smoking interaction.

Table 15. Joint effects between income-mediators and mediator-mediator in 53,632 participants in eight cohort studies in Finland

Minimally-adjusted model plus:	Category	Additional alcohol-attributable deaths per 10,000 person-years	95% CI
Income, alcohol use and interaction term	Lowest vs highest income quintile	0.9	-1.1; 2.8
	High alcohol intake vs never or former drinker	23.1	14.2; 31.8
	Interaction lowest income*High alcohol intake	46.8	25.0; 68.6
Income, smoking and interaction term	Lowest vs highest income quintile	1.2	-0.3; 2.7
	Current smoker vs. never smoker	7.7	4.3; 11.0
	Interaction lowest income*Current smoker	11.4	5.8; 17.0
Income, BMI and interaction term	Lowest vs highest income quintile	6.6	4.0; 9.2
	Obese vs. normal weight	4.1	-0.02; 8.1
	Interaction lowest income*Obese	-4.2	-9.8; 1.4
Alcohol use, smoking and interaction term	High alcohol intake vs never or former drinker	28.6	18.0; 39.2
	Current smoker vs never smoker	6.9	4.7; 9.1
	Interaction high alcohol intake*current smoker	12.3	-1.3; 25.9
Alcohol use, BMI and interaction term	High alcohol intake vs never or former drinker	38	28.4; 47.6
	Obese vs normal weight	1.1	-0.6; 2.8
	Interaction high alcohol intake*Obese	-0.7	-18.1; 16.7

Minimally-adjusted model is adjusted for sex, age (as timescale), survey round and marital status. The model includes the two factors and their interaction term. High alcohol intake was defined as ≥252 g/wk in men and ≥168 g/wk in women. Obese was defined as >30 kg/m^2 and normal weight as 18.5-30 kg/m^2.

The results of the causal mediation analysis (Table 16) show that participants in the lowest income quintile had 5.5 additional alcohol-attributable deaths per 10,000 person-years compared to those in the highest income quintile. The direct effect of income on alcohol-mortality was 8.3 additional alcohol deaths per 10,000 person years and the indirect effect through the mediators

and their additive interactions was -2.8 additional alcohol deaths per 10,000 person-years (95% CI, -3.8; -1.8). This means that the indirect effect is partially masking the effect of income on alcohol-attributable mortality.

The proportion mediated by alcohol use was negative (-69.3%), out of which -22.1% was attributable to the indirect effect of income through alcohol use (differential exposure) and -47.2% was attributable to the mediated interactive effect of income and alcohol use (differential vulnerability). In terms of a hypothetical intervention, a change in the level of alcohol use from the lowest income quintile to the highest income quintile (i.e. prevalence of heavy volume drinking would increase from 3.7% to 7%), this would result in a 69.3% increase in alcohol-attributable deaths in the lowest income quintile.

The proportion mediated by smoking and BMI was 18.1%. The indirect and mediated interactive effects of BMI cancelled each other, resulting in the effect being driven by the indirect effect of smoking (9.2%, i.e. differential exposure) and the mediated interactive effect of smoking (8.4%, i.e. differential vulnerability). Overall, all the effects of smoking and obesity explained 18.1% of the total effect of income on alcohol-attributable mortality.

Table 16. Total, direct, indirect and mediated interactive effects of income on alcohol-attributable mortality in 53,632 participants in eight cohort studies in Finland

	Additional alcohol-attributable deaths per 10,000 person-years		Proportion explained[1]	
Effect	**Estimate**	**95% CI**	**Estimate**	**95% CI**
Total effect[2]	5.5	3.7; 7.3	100	
Direct effect	8.3	6.0; 10.6	151.3	133.5; 177.7
Indirect effects combined	-2.8	-3.8; -1.8	-51.3	-85.0; -30.9
Indirect effects by mediator				
Alcohol use				
Indirect effect	-1.2	-2.0; -0.4	-22.1	-43.0; -7.3
Mediated interactive effect[3]	-2.6	-3.8; -1.4	-47.2	-72.2; -27.3
Smoking				
Indirect effect	0.5	0.3; 0.7	9.2	4.8; 16.2
Mediated interactive effect[3]	0.5	0.1; 0.8	8.4	1.7; 15
BMI				
Indirect effect	0.4	0.1; 0.8	7.9	1.5; 16.9
Mediated interactive effect[3]	-0.4	-0.9; 0.1	-7.4	-18.9; 1.4

The model is from a marginal structural model additive hazard model that removes confounding by sex, age (as timescale), survey round and marital status. 1. Proportion explained is the ratio between the effect and the total effect multiplied by 100. 2. Total effect is the sum of direct effects and the effects of the mediators. 3. Mediated interactive effects are the effects mediated through the income-mediator interaction.

6 Discussion

6.1 SUMMARY OF THE MAIN FINDINGS

This study examined the socioeconomic differences in alcohol use, alcohol use disorders and alcohol-related harm and explored potential explanations for the alcohol harm paradox.

We observed the existence of socioeconomic differences for several indicators of alcohol use in Finland and Chile. Abstinence was higher among lower socioeconomic groups in both countries. These inequalities in Finland were more prominent among participants aged 45 to 64 years old, while in Chile they were more prominent among women. Inequalities in weekly volume of alcohol use and heavy volume drinking were less marked. In Finland, lower SES was associated with higher weekly volume of alcohol use and heavy volume drinking among men aged 25 to 44 years old; conversely, weekly volume of use and heavy volume drinking was higher among higher SES men and women aged 45 to 64. These inequalities were overall quite small. In Chile, higher SES women aged 45 to 64 years old showed higher weekly volume of alcohol use and heavy volume drinking. Heavy episodic drinking was higher among lower socioeconomic groups overall and in all subgroups in Finland. In Chile, results were inconclusive. The distributions of the same alcohol use indicators in section 5.4 (using data from eight Finnish population surveys) are consistent with these results.

Estimated prevalence of 12-month alcohol use disorders in Finland decreased from 4.6% in 2000 to 2.0% in 2011. Alcohol use disorders were more prevalent among those with intermediate education. We observed a reduction in the prevalence of AUD from 2000 to 2011 in all educational groups. Both in 2000 and 2011, we did not find evidence of educational difference in 12-months AUD after adjusting for covariates. Selection bias and information bias appear to partly explain these results.

We observed marked socioeconomic differences in alcohol-attributable mortality in Finland, which persisted after adjusting for sociodemographic variables and using either income or education as indicators of socioeconomic status. In the same dataset, we observed that those with higher income and education had higher rates of weekly volume of alcohol use, heavy

volume drinking and heavy episodic drinking. This shows the existence of the alcohol harm paradox in Finland.

Finally, we explored two potential explanations for the alcohol harm paradox: measurement error from information bias derived from self-report of alcohol use and joint effects between SES, alcohol use, obesity and body mass index. Using alcohol biomarkers, we showed that biomarkers were associated with alcohol-attributable mortality and improved the predictive ability when used in conjunction with self-report alcohol use. This suggests alcohol biomarkers have a complementary value to self-reported alcohol use. The analyses showed, however, that alcohol biomarkers, used alone or together with self-reported alcohol use, explained a very small proportion of the socioeconomic differences in alcohol-attributable mortality in our data.

Likewise, we found evidence of joint effects between the lowest income quintile and alcohol use and, in addition, smokers were more vulnerable to dying from alcohol-attributable causes. However, our results show that smoking, body mass index and their additive interactions with SES explained only a relatively small proportion (18.1%) of the association between income and alcohol-attributable mortality.

6.2 SOCIOECONOMIC DIFFERENCES IN ALCOHOL USE

We found a higher prevalence of abstinence among lower socioeconomic groups. This is consistent with findings from previous studies in high-income countries (Bloomfield, et al., 2006, Grittner, et al., 2012, Sassi, 2015, van Oers, et al., 1999). This may be because alcohol is less affordable for lower socioeconomic groups, as their disposable income is lower, and they have to prioritize covering their basic needs.

We observed a more complex picture regarding socioeconomic differences in weekly volume of alcohol use and heavy volume drinking. In Finland, the magnitude of the socioeconomic differences was rather small when we used data from 2008-2010 in Sub-study I, consistent with previous studies in Europe and the United States (Bloomfield, et al., 2000, Bloomfield, et al., 2006, Giskes, et al., 2011, Helasoja, et al., 2007, Karriker-Jaffe, et al., 2012). However, there was a clear gradient (higher socioeconomic groups showed higher weekly volume of alcohol use) in the data from 1978-2007 in Sub-studies III and IV. This suggests that socioeconomic differences in volume of alcohol use might have reduced over time. This is consistent with studies examining secular trends in Finland (with AVTK data) and Sweden,

which generally suggest that the explanation for this reduction is an increase in consumption among lower socioeconomic groups (Combes, et al., 2011, Helakorpi, et al., 2010). In Chile, there was an overall higher volume of alcohol use among those with higher education, which was more pronounced among women aged 45 to 64 years old. This has also been described in studies in the United States, OECD countries and some countries of the GENACIS study (Bloomfield, et al., 2006, Lui, et al., 2018, Sassi, 2015), while other studies have not found differences (van Oers, et al., 1999). One possible explanation may be changes in social norms, where alcohol use could be considered a sign of independence and empowerment. This, in part, could be a direct effect of targeted alcohol marketing at women in that age range, promoting and/or reinforcing such ideas (Atkinson, et al., 2019).

Our results show that, in Finland, the prevalence of heavy episodic drinking was higher among those with lower education using data from 2008-2010 in Sub-study I. The magnitude of the difference in our study was, however, very small. These findings are in line with the causal estimates using Mendelian randomization in the UK Biobank (Rosoff, et al., 2019) and previous studies in the United States (Giskes, et al., 2011, Harper and Lynch, 2007, Midanik and Clark, 1994), Germany (van Oers, et al., 1999) and Finland (Paljärvi, et al., 2012). HED was more prevalent in higher income groups when using data from 1978-2007 in Sub-studies III and IV. This may indicate, again, that socioeconomic inequalities in HED might have changed over time.

Additional sensitivity analyses showed that excluding 12-month abstainers resulted in an upward correction of the weekly volume of alcohol use, heavy volume drinking and HED in both countries. However, these changes did not affect our estimates of socioeconomic differences (i.e. the concentration index), except for heavy volume drinking in Chilean men aged 25-44, where the estimate became negative.

6.3 PREVALENCE AND SOCIOECONOMIC DIFFERENCES IN ALCOHOL USE DISORDERS

We estimated a reduction in the prevalence of alcohol use disorders between 2000 and 2011. This result was unexpected given the rise in alcohol use following the reduction in alcohol taxes in 2004 and the increase in alcohol-attributable mortality until 2007 (Herttua, et al., 2008). One explanation is that the described reduction is a result of a combination of selection bias due to

lower participation in 2011 and information bias due to the re-testing of the same participants. Selection bias is plausible considering that using multiple imputation resulted in an increase in 1 percentage point in lifetime AUD and the prevalence of lifetime hospitalizations due to alcohol dependence was higher among non-participants. However, we observed these in both 2000 and 2011, suggesting that prevalence of AUD was underestimated in both surveys. Information bias is another possible explanation for the estimated prevalence reduction. We found some support for this in the observed reduction of lifetime AUD among the same participants in 2000 and 2011.

On the contrary, there are some indications that a true reduction in prevalence of AUD could be possible. In our data, the decrease in prevalence of AUD occurred also in the group of 30-41 years olds; including those who were in that age group in 2011 and did not participate in the CIDI in 2000. These participants were not affected by a possible re-testing bias, although the reduction, however, could potentially be attributed to changes in the way AUD questions were asked in 2011 (see section 4.3.5). Reductions of AUD prevalence have been reported elsewhere, in studies in Australia (Teesson, et al., 2010), United Kingdom (Fuller, et al., 2009) and a US study using a comparable version of CIDI (Kessler, et al., 2005, Kessler, et al., 1994). In Finland, deaths due to alcohol dependence have remained stable and hospitalizations due to alcohol dependence decreased by 30% during the study period (Finnish Institute for Health and Welfare, 2014, Statistics Finland, 2017), lending credence to a possible true reduction in AUD prevalence. Unfortunately, the latest population health survey in Finland did not include the CIDI, leaving these questions open (Borodulin and Sääksjärvi, 2019).

We found no useful evidence on educational differences in AUD in 2000 nor in 2011, as our confidence intervals indicate a wide range of plausible associations. This is somewhat surprising given the clear socioeconomic patterning of alcohol-attributable mortality, but the precision of our estimates is low. Similar results have been described in studies in Norway (Kringlen, et al., 2001), ten European countries (Pinto-Meza, et al., 2013) and the United States (Karriker-Jaffe, et al., 2012), which also lacked statistical power to obtain more precise estimates. This indicates the need for larger sample sizes of studies aimed to assess socioeconomic differences in AUD, or the need for using individual participant data meta-analysis from several studies to increase precision.

6.4 SOCIOECONOMIC DIFFERENCES IN ALCOHOL MORTALITY

We confirmed the existence of income and educational differences in alcohol-attributable mortality. The magnitude of this difference is somewhat smaller than in other survey-based studies, for example, the hazard ratio was 4.1 comparing unskilled manual workers versus higher non-manual workers in Sweden (Sydén, et al., 2017) and 4.4 comparing lowest versus highest income quintiles in Scotland (Katikireddi, et al., 2017). This may be because of the composition of our surveys, where older surveys predominate in our analyses (due to longer follow-up and deaths) and socioeconomic differences might have increased over time. For instance, a Finnish study using data from surveys in 1968, 1976 and 1984 found a hazard ratio of 2.1, a similar estimate to our study (Mäkelä and Paljärvi, 2008). Selection bias due to non-participation of individuals with higher risk of alcohol-attributable mortality could also explain a smaller magnitude of the association. Excluding never and former drinkers resulted in an increase in hazard ratios for all income quintiles (compared to the highest income quintile). This increase was proportionately higher in the lowest socioeconomic quintile, reflecting the higher proportion of never and former drinkers in lower socioeconomic groups. In the data for Sub-study III, never and former drinkers had lower (but nonetheless considerable) rates of alcohol-attributable mortality, suggesting the existence of misclassification bias in this category. In a study in Sweden, abstainers had two times higher risk of alcohol-attributable events than light drinkers (HR 2.0, 95% CI 1.3; 3.2) and 2.5 times higher risk of alcohol-attributable events than drinkers without HED (HR 2.5, 95% CI 1.6; 4.0) (Sydén, et al., 2017). In a Danish study, male abstainers had higher risk of alcohol-attributable mortality than light drinkers (1-7 doses per week), while there was no evidence of increased risk among female abstainers (Nordahl, et al., 2017). This indicates that the risk of alcohol-attributable mortality among never and former drinkers might differ substantially in different population health surveys.

6.5 ALCOHOL HARM PARADOX

We confirmed the existence of the alcohol harm paradox in the Finnish population. When we excluded never and former drinkers, the socioeconomic gradient tended to disappear, and the lowest and highest income quintile reported very similar levels of volume alcohol use. However,

these similar levels of alcohol use were still in contrast with clear socioeconomic differences in alcohol-attributable mortality. Comparison with previous studies is limited, as few studies have been able to measure both alcohol use and alcohol-attributable mortality in the same participants. In a Swedish study, the prevalence of heavy volume drinking was 14.5% for unskilled workers and 12.4% for higher non-manual employees, which was small compared to the large difference in alcohol-attributable mortality (Sydén, et al., 2017). Similar to our findings, a recent study in Scotland found higher prevalences of heavy volume drinking, excessive volume drinking and heavy episodic drinking among those in the highest income category. For example, 24.8% of the highest income quintile were heavy volume drinkers compared to 10.9% in the lowest income quintile, with a clear socioeconomic gradient (Katikireddi, et al., 2017).

6.6 EXPLANATORY FACTORS

Comparison with previous studies is, again, limited as to our knowledge no study has examined whether differential bias in the measurement of exposure or joint effects between behavioural risk factors can explain the alcohol harm paradox.

We showed that using alcohol biomarkers provided additional information, but explained only a small proportion of the socioeconomic differences in alcohol-attributable mortality. These findings lend credence to previous research showing that self-reported alcohol use explained a small proportion of socioeconomic differences in alcohol-attributable mortality. In line with our findings, a study in Finland using data from the Finnish Drinking Habits Survey 1968, 1976 and 1984, found that hazard ratios attenuated minimally or increased after adjusting for several measures of alcohol use (Mäkelä and Paljärvi, 2008). Similarly, a study in Scotland found that the hazard ratio experienced a small reduction after adjusting for volume of alcohol use and HED among those without education and unskilled workers and increased among those from most deprived areas and the lowest income quintiles (Katikireddi, et al., 2017). A Swedish study found a larger attenuation of 24% after adjusting for volume of alcohol use and HED in unskilled manual workers (HR decreased from 4.1 to 2.9), and similar reductions among skilled workers and lower non-manual employees, in comparison with higher non-manual employees (Sydén, et al., 2017). The results of our study show that differential bias in the measurement of exposure is an unlikely explanation for the alcohol harm paradox.

Our results confirmed the existence of joint effects between income and alcohol use on alcohol-attributable mortality. This is consistent with previous studies in Finland, Scotland and Denmark. In Finland, the aforementioned study using data from the Finnish Drinking Habits Surveys provided visual evidence of an additive interaction between occupational class and alcohol use on alcohol-attributable events (i.e. hospitalizations and deaths). In the aforementioned Scottish study, there was evidence of a joint effect between SES and alcohol use for all four socioeconomic indicators used (education, income, occupational class and area-based deprivation). A Danish study examined the potential joint effect using additive hazard models and found 28.9 extra events due to the interaction (per 10,000 person-years) among men and 23.9 among women (Nordahl, et al., 2017). Lower socioeconomic groups appear to experience disproportionately greater alcohol-attributable harm at the same levels of alcohol use.

We found joint effects between income and smoking, but not between alcohol and smoking and alcohol and BMI. In the case of the alcohol-smoking interaction, the confidence intervals were mostly compatible with an additive interaction, but the statistical power was likely insufficient.

The results of the causal mediation analysis (Sub-study IV) showed, however, that the mediated effects between income and smoking and income and BMI explained a relatively small proportion, 18.1%, of the socioeconomic differences in alcohol-attributable mortality. In the Scottish study discussed above, the authors observed a relatively small reduction in the HRs after adjusting for alcohol use, HED, smoking status and BMI. For example, the HR in the lowest income quintile decreased from 4.4 to 3.6 and from 3.8 to 2.5 in the lowest educational group (ISCED 0) (Katikireddi, et al., 2017). In the Swedish study discussed above, adjusting for several measures of alcohol use and smoking resulted in a larger attenuation of the HR than in our study, from 4.1 to 2.4 (percent attenuation 37.4%) (Sydén, et al., 2017). These findings are equivalent to a total indirect effect (PIE+INTmed), and in our study we were able to decompose the proportion explained by differential exposure and differential vulnerability. The observed mediated effect of smoking on alcohol-attributable mortality, given that alcohol is a necessary cause, could be due to unmeasured harmful drinking (given alcohol use and smoking are strongly correlated) or to combined effects that were not captured by the alcohol-smoking interaction.

The direct effect of socioeconomic status on alcohol-attributable mortality in our study remained largely unexplained. Taken together, the results of our study suggest that differential vulnerability is a key component of the alcohol harm paradox. Other potential mechanisms (i.e.

mediators) that can explain this direct effect of socioeconomic status include differential diets, higher cumulative disadvantage (including adverse childhood events) and stress among lower socioeconomic groups, differential environmental factors and differential access to health care. We cannot rule out the existence of reverse causality in our data, although the sensitivity analyses using education as a socioeconomic indicator showed similar results to the main analysis described in section 5.5.2. Education is less prone to reverse causality, unless alcohol-related problems are early and severe enough to disturb the person's educational attainment (see section 6.7.1).

6.7 THREATS TO VALIDITY

As in any epidemiological research, this study is subject to limitations due to several threats to validity. This section is structured using Shadish, Cook and Cambell's typology of validity, discussed and adapted for epidemiological studies by Matthay and Glymour (Matthay and Glymour, 2020). Not all items are discussed, only the ones that are relevant to the study design and research questions.

6.7.1 INTERNAL VALIDITY

Selection bias. The study used data from several population health surveys, which are subject to selection bias due to non-participation. Selection bias arises from systematic differences between participants and non-participants and can threaten both internal and external validity.

Non-participation can threaten internal validity when the relative socioeconomic differences in alcohol use, AUD and alcohol-attributable mortality are distorted. In other words, non-participation might bias the exposure-risk associations. Although research consistently shows that non-participation can lead to underestimated prevalence rates and reduce the magnitude of associations (see section 2.3.1), studies comparing participants versus the total population have shown that the socioeconomic gradient has been similar for smoking status (Van Loon, et al., 2003), alcohol abuse (Osler, et al., 2008), sickness absence (Martikainen, et al., 2007), and all-cause mortality (Ferrie, et al., 2009, Harald, et al., 2007). Other studies have shown evidence of distortion on the estimation of social gradients of poor subjective health (Lorant, et al., 2007) and alcohol-related outcomes (Gorman, et al., 2014, McMinn, et al., 2020). Given the available

evidence, we cannot rule out that selection bias could have affected our exposure-risk associations in all sub-studies, but the magnitude of the bias is likely to be small.

Confounding. Sub-studies I and II are descriptive studies and the results were either disaggregated or adjusted by sex and age (and marital status and level of education in Sub-study II). Estimates in Sub-study III were additionally adjusted for smoking and body mass index, poor self-rated health and several baseline health conditions (see section 4.3.3). There are, however, many other potential confounders that were not considered in the study. At the individual level, these include adverse life events and parental socioeconomic position, among others (Kestilä, et al., 2008, Loucks, et al., 2012, Nandi, et al., 2012).

Our results could also be confounded by secular trends due to, for example, national alcohol policies and economic conditions that affected alcohol availability. We partially accounted for this by adjusting for survey round using random effects (included as a shared frailty) in Sub-study III, and as a fixed effect in Sub-study IV.

Ambiguous temporal precedence. Sub-study I is a cross-sectional study and therefore does not allow to disentangle whether alcohol use precedes the educational level or vice versa. In Sub-studies III and IV, as cohort studies linked to mortality, there is clear temporal distinction between exposure and outcome. However, we cannot disentangle the temporal precedence of socioeconomic status and behavioural risk factors. We have assumed that socioeconomic status precedes the behavioural risk factors, which was explicit in the directed acyclic graph in Sub-study IV (see Figure 4). We have used socioeconomic indicators (household income and education) that are less sensitive to reverse causality (i.e. that alcohol use precedes and causes socioeconomic status) (Valkonen, 1993), but it cannot be ruled out.

6.7.2 CONSTRUCT VALIDITY

Re-testing bias. The reassessment of individuals is subject to re-testing bias, where participants respond to the same questions differently at different time points. In Sub-study II, we reassessed participants in 2000 and 2011 and observed a reduction in lifetime prevalence of AUD. In this case, this difference could have happened due to failure to remember past events or reduced interest to report their alcohol use and AUD symptoms in 2011, either due to interview fatigue, denial or social desirability. Similar inaccuracies in lifetime prevalences have been reported for

other mental disorders (Takayanagi, et al., 2014) and could explain the reduction in lifetime prevalence reported in our study.

Information bias. We used instruments to measure socioeconomic status and behavioural risk factors that have been extensively used in previous studies. In Sub-study II, the M-CIDI has excellent psychometric properties for diagnosing alcohol use disorders, although it was tested in a younger population than the one in our study (Lachner, et al., 1998, Wittchen, et al., 1998).

In Sub-study III, we explored explicitly the potential role of alcohol biomarkers to account for the possibility of information bias (i.e. measurement error of the alcohol use indicators). Our results suggest that, while alcohol biomarkers provided additional information when used together with self-reported alcohol use, they explained a small proportion of the socioeconomic differences in alcohol-attributable mortality. This suggests that even if there is information bias, this is likely distributed evenly across socioeconomic groups. However, it should be noted that, as described in Table 1, the indirect alcohol biomarkers used in the study provide information of a relative narrow time frame (weeks to few months) and they were measured at one time point on average 20 years before the end of follow-up. In sensitivity analyses in the Sub-studies III and IV, restricting follow-up times to 10, 20 and 30 years did not change the main results. This suggests that changes in alcohol use and alcohol biomarkers over time likely do not have a great impact on the results of these sub-studies.

In Sub-studies III and IV, the associations between SES and alcohol-attributable mortality could potentially be explained by differential misclassification bias of the outcome. In other words, the death certification process could be vulnerable to bias (e.g. from physicians) that would make them more likely to assign an alcohol-attributable ICD code to lower socioeconomic groups (Mäkelä, 1999). We consider this risk of bias as potentially small, since, as discussed in section 4.3.6, the quality of the death register in Finland is very high and undergoes an extensive validation process.

6.7.3 STATISTICAL VALIDITY

Violation of assumptions. The statistical models used in the study rely on several assumptions that need to hold to obtain valid estimates.

In Sub-study I, the calculation of the concentration index requires a socioeconomic indicator with an equal difference between the values. While our socioeconomic variable (i.e. years of

education) generally fulfils this requirement, it could be argued that attained qualifications (e.g. high school graduation) make a greater difference in the future socioeconomic status of the respondent than another additional year of education.

In Sub-study II, we assumed for the multiple imputation that data was missing at random (MAR), which means that the probability of missingness is the same within groups defined by the observed data (van Buuren, 2018). Even though we used a large set of variables, we cannot rule out that the probability of missing might vary by reasons not known to us, making the data missing not at random (MNAR). Likewise, in Sub-studies I, III and IV, we used complete case analysis which assumed that the probability of missing is the same for all cases (i.e. missing completely at random, MCAR). This is a strict assumption and we cannot rule out that it influenced the results. However, at the time of analyses I considered that it was not technically feasible to apply multiple imputation. In Sub-study I, we used a hand-written package in Stata that was not able to handle multiple imputation. In Sub-study III, the final models were complex, incorporating complex survey design, smoothing splines and time interactions to account for the violation in the proportional hazards assumption, leading to singular fit issues in some cases. In Sub-study IV, the dataset was expanded 125 times and the final analyses with robust errors took more than ten days to run.

In Sub-study IV, as discussed in section 4.4., the causal interpretation of the mediation analysis requires a set of strong assumptions to hold, where we must assume there is no unmeasured confounding between SES and alcohol mortality, SES and behavioural risk factors and behavioural risk factors and alcohol mortality (Imai, et al., 2010, VanderWeele, 2016). While we controlled for important confounders, we cannot rule out the existence of unmeasured confounding, for example, due to adverse childhood events or genetic factors. While the method has clear benefits over traditional mediation analysis as it facilitates a decomposition of the different effects, a causal interpretation of the results is not possible.

6.7.4 EXTERNAL VALIDITY

Selection bias. Selection bias can threaten external validity if it impairs the representativeness of the target population (see section 2.1.3). In our study, the sampling frame used in Sub-studies I-IV comes from the Population Register of Statistics Finland, which has few missing elements and a very high coverage. The sampling frame of the Chilean National Health Survey comes from the National Institute of Statistics and has a small number of duplicates or non-eligible

listings but excludes people living in non-residential households. We, therefore, consider the effect of this bias to be small.

Another important selection bias comes from non-participation. As discussed in section 2.1.3, non-respondents are more often younger, male, of low socioeconomic status and divorced or widowed. These population groups have probably higher prevalence of heavy drinkers or heavy episodic drinkers, and as a consequence, it could have resulted in an underestimation of the absolute values of our indicators (Zhao, et al., 2009). Specifically, (i) in Sub-study I, non-participation could underestimate the absolute level of alcohol use; (ii) in Sub-study II, the prevalence of AUD could be underestimated; (iii) in Sub-studies III and IV, the absolute levels of smoking and volume of alcohol use could be underestimated, as well as the absolute levels of alcohol-mortality.

In Sub-study II, we used inverse probability weights and multiple imputation to account for non-participation bias. Using multiple imputation resulted in higher prevalence estimates in both 2000 (when participation rate was 79.6%) and 2011 (participation rate was 59%), although the change was modest. This suggests that both prevalence estimates could have been underestimations, which is consistent with previous research on non-participation and alcohol-related outcomes (Gorman, et al., 2014, Jousilahti, et al., 2005, Maclennan, et al., 2012, McMinn, et al., 2020, Tolonen, et al., 2019).

Transferability to other settings. This study was carried out using data from Finland in all sub-studies and Chile in Sub-study I. Our results are likely transferable to similar settings as Finland, especially high-income countries with high levels of socioeconomic differences in alcohol-attributable mortality. In Europe this includes Denmark, Scotland, Slovenia, Hungary, Lithuania and Estonia (Mackenbach, et al., 2015). The similarities observed in the socioeconomic inequalities in alcohol use between Finland and Chile lend support to the interpretation that our findings might be transferable to other countries of high consumption and high alcohol-related harm.

Transferability should also consider the characteristics of the populations in the study. This study has a good representation of the working-aged population aged 30 to 64 years old, as well as those 65 and over in Sub-study II and in some cohorts in Sub-studies III and IV (see section 4.2).

6.8 PUBLIC HEALTH IMPLICATIONS

Harmful alcohol use impacts health and societal wellbeing; these negative effects are socially patterned and experienced greatly by those in lower socioeconomic groups. Reducing this burden is desirable for societies at large and effective public policies are needed for this purpose.

A salient point is the need for regular monitoring and reporting of socioeconomic differences in alcohol use, disorders and harm by statistical agencies in Finland. Current regular reporting, for example in the Yearbook of Alcohol and Drugs Statistics by the Finnish Institute for Health and Welfare or the report on Causes of Death by Statistics Finland, includes disaggregated data by gender and age, but not socioeconomic status (Finnish Institute for Health and Welfare, 2019, Statistics Finland, 2018). Research articles are a good source of information on socioeconomic differences of alcohol use, disorders and harm; however, their availability is dependent on the interest of the research community, their results take time to be analysed and published, they provide information on specific population groups and rely on methods that might not be comparable with other studies. Regular reporting by statistical agencies is crucial to provide timely and comparable data on socioeconomic differences.

Our results suggest that low socioeconomic groups are more vulnerable to the effects of alcohol and smoking on alcohol-attributable mortality. This supports the need for a strategy to reduce health inequalities combining universal and targeted policy approaches, which has been called "proportionate universalism" (Marmot, 2010). Universal alcohol and tobacco policies, such as raising taxes and introducing minimum unit pricing, reducing availability and restricting marketing are examples of universal policies shown to yield greater benefits to lower socioeconomic groups (Anderson, et al., 2009, Mäkelä, et al., 2015, Wood and Bellis, 2017). Targeted approaches to reduce alcohol-attributable harm among lower socioeconomic groups include providing greater coverage of brief alcohol interventions and access to treatment for alcohol-related conditions to lower SES communities or individuals (Loring, 2014). Policy initiatives can also aim to reduce alcohol availability or marketing in lower socioeconomic areas. As these targeted approaches can be seen as stigmatising and interfering with civil rights and face resistance from alcohol outlet owners, it is essential to actively involve communities and local actors in the planning and implementation of such policies. In many countries, these initiatives can be implemented by subnational units, such as cities or municipalities, which might already have programmes and knowledge on effective community participatory processes

(Anderson, et al., 2018). An additive interaction reinforces the idea that scarce resources are better invested in targeted approaches to lower socioeconomic groups.

In addition, our findings support that differential vulnerability might play a greater role than differential exposure in the socioeconomic differences in alcohol-attributable harm. Rather than focusing solely on behavioural risk factors, these results confirm the need to address structural determinants of health (social, commercial, environmental, and political) as well as safety nets that would support vulnerable populations in need.

7 Conclusions

This study contributed to the existing body of literature examining the socioeconomic differences in alcohol use, disorders and harm and the quest for explanations of the alcohol harm paradox. Using methods that incorporated the whole socioeconomic spectrum, we observed higher levels of alcohol abstinence among lower socioeconomic groups and modest socioeconomic differences in volume of alcohol use and heavy episodic drinking in Finland. Accounting for measurement error in alcohol use with alcohol biomarkers did not seem to explain the socioeconomic differences in alcohol-attributable mortality. Taken together, these findings confirmed the alcohol harm paradox in Finland and suggest that differential bias in the measurement of alcohol use is not a likely explanation of the alcohol harm paradox. In addition, we found that alcohol use disorders might not be socially patterned.

These results extend the alcohol harm paradox, by suggesting that the explanation of the socioeconomic differences in alcohol-attributable harm might not lie in the differential exposure to alcohol, nor in the differential incidence of alcohol-attributable conditions. Further research could build on this, starting from examining socioeconomic differences in the prevalence of other alcohol-attributable conditions and advancing to explore the socioeconomic differences in incidence estimates using longitudinal designs.

The observed joint effects between SES and alcohol use and SES and smoking indicate that lower socioeconomic groups are more vulnerable to the effects of alcohol use and smoking. However, accounting for behavioural risk factors and their joint effects explained less than 20% of the socioeconomic differences in alcohol-attributable mortality.

Further studies could explore whether our findings hold in settings different than Finland and Chile and examine other potential mediators of the effect of SES on alcohol-attributable mortality, including different forms of stress (e.g. work-related or due to adverse life events), diet and access to health care. Exposure to behavioural risk factors could be better assessed, using e.g. more precise indicators of smoking (such as number of cigarettes smoked per day or biomarkers like cotinine) or obesity, as well as using longitudinal datasets with repeated measures to incorporate information of trajectories of alcohol use, smoking and obesity. As differential vulnerability appears to have a central role in the alcohol harm paradox, research exploring the different dimensions of vulnerability (e.g. family, school, intergenerational

transmission, personality traits) could potentially provide valuable information. This can also include multilevel analyses exploring the role of environmental factors such as the differential alcohol availability and marketing.

Future research could also examine the potential impact of the reduction of drinking in adolescents and young adults observed in several developed countries (including Finland) (Callinan, et al., 2020, Oldham, et al., 2020, Pape, et al., 2018, Raitasalo, et al.) on socioeconomic differences in alcohol-attributable harm. In addition, studies examining the impact of universal and targeted alcohol policies and interventions on socioeconomic differences in alcohol-attributable harm could be important to understand what works in reducing these differences.

Our causal mediation analysis in Sub-study IV was an attempt to move from estimating associations to assessing causal effects. As these analyses are constrained by assumptions unlikely to be met (see section 6.7.3), further studies could use sources of exogeneity to provide stronger estimation of causal effects. These include the use of instrumental variable designs, such as Mendelian randomization, to remove the residual confounding from observational studies (Rosoff, et al., 2019), or natural experiments as sources of external variation on socioeconomic status (Glied, et al., 2012, Matsuyama, et al., 2017). Changes in educational or social policies, such as compulsory schooling policies or cash transfers (Avendaño, et al., 2020, Fenney, 2017, Heckley, et al., 2020), could provide exciting opportunities to examine the causal effect of socioeconomic status on alcohol-attributable harm.

8 Appendix

Table A1. Concentration index for weekly volume drinking in Finland and Chile excluding 12-month drinkers

Weekly volume drinking	Whole population			Excluding 12-month abstainers		
	Concentration index	95% CI		Concentration index	95% CI	
Finland						
Overall	-0.01	-0.03	0.01	-0.04	-0.07	0.003
Men 25-44	-0.04	-0.07	-0.01	-0.11	-0.19	-0.04
Men 45-64	0.05	0.02	0.08	0.04	-0.02	0.11
Women 25-44	0.003	-0.03	0.04	-0.04	-0.15	0.06
Women 45-64	0.06	0.03	0.09	0.07	-0.02	0.16
Chile						
Overall	0.13	0.04	0.23	0.04	-0.04	0.11
Men 25-44	0.05	-0.04	0.15	-0.06	-0.13	0.01
Men 45-64	0.17	-0.05	0.39	0.104	-0.06	0.27
Women 25-44	0.03	-0.15	0.21	-0.06	-0.19	0.08
Women 45-64	0.26	0.14	0.38	0.21	0.07	0.35

Table A2. Concentration index for heavy volume drinking in Finland and Chile excluding 12-month drinkers

Heavy volume drinking	Whole population			Excluding 12-month abstainers		
	Concentration index	95% CI		Concentration index	95% CI	
Finland						
Overall	-0.01	-0.05	0.03	-0.04	-0.07	0.003
Men 25-44	-0.11	-0.19	-0.03	-0.11	-0.19	-0.04
Men 45-64	0.06	-0.002	0.12	0.04	-0.02	0.11
Women 25-44	-0.04	-0.14	0.07	-0.04	-0.15	0.06
Women 45-64	0.11	0.02	0.19	0.07	-0.02	0.16
Chile						
Overall	0.04	-0.21	0.3	-0.07	-0.19	0.05
Men 25-44	0.07	-0.43	0.57	-0.27	-0.48	-0.07
Men 45-64	0.07	-0.34	0.47	0.002	-0.24	0.24
Women 25-44	-0.34	-0.71	0.03	-0.18	-0.43	0.07
Women 45-64	0.47	0.18	0.75	0.51	0.22	0.80

Table A3. Concentration index for heavy episodic drinking in Finland and Chile excluding 12-month drinkers

Heavy episodic drinking	Whole population			Excluding 12-month abstainers		
	Concentration index	95% CI		Concentration index	95% CI	
Finland						
Overall	-0.10	-0.13	-0.08	-0.14	-0.16	-0.07
Men 25-44	-0.10	-0.16	-0.05	-0.12	-0.18	-0.03
Men 45-64	-0.06	-0.1	-0.01	-0.09	-0.14	-0.02
Women 25-44	-0.10	-0.16	-0.04	-0.11	-0.18	-0.04
Women 45-64	-0.10	-0.16	-0.05	-0.15	-0.20	-0.07
Chile						
Overall	-0.04	-0.14	0.07	-0.12	-0.18	-0.05
Men 25-44	-0.12	-0.31	0.06	-0.18	-0.28	-0.05
Men 45-64	-0.07	-0.22	0.09	-0.16	-0.26	-0.03
Women 25-44	-0.14	-0.39	0.11	-0.19	-0.32	-0.04
Women 45-64	-0.07	-0.43	0.28	-0.02	-0.23	0.17

9 References

Aalen O, Scheike TH. Aalen's additive regression model. In: Armitage P & Colton T, editors. Encyclopedia of Biostatistics: Wiley & Sons; 2005.

Adler NE, Newman K. Socioeconomic disparities in health: Pathways and policies. Health Aff 2002; 21: 60-76.

Ågren G, Romelsjö A. Mortality in alcohol-related diseases in Sweden during 1971–80 in relation to occupation, marital status and citizenship in 1970. Scand J Public Health 1992; 20: 134-142.

Alatalo PI, Koivisto HM, Hietala JP, Puukka KS, Bloigu R, Niemelä OJ. Effect of moderate alcohol consumption on liver enzymes increases with increasing body mass index. Am J Clin Nutr 2008; 88: 1097-1103.

Allen LN, Townsend N, Williams J, Mikkelsen B, Roberts N, Wickramasinghe K. Socioeconomic status and alcohol use in low- and lower-middle income countries: A systematic review. Alcohol 2018; 70: 23-31.

American Psychiatric Association. Diagnostic and statistical manual of mental disorders, DSM-IV, 4th ed. Arlington, United States: American Psychiatric Publishing; 1994.

American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-5, 5th ed. Arlington, United States: American Psychiatric Publishing; 2013.

Anderson P, Chisholm D, Fuhr DC. Effectiveness and cost-effectiveness of policies and programmes to reduce the harm caused by alcohol. Lancet 2009; 373: 2234-2246.

Anderson P, Jané-Llopis E, Hasan O, Rehm J. City-based action to reduce harmful alcohol use: Review of reviews. F1000Research 2018; 7.

Andréasson S, Danielsson AK, Hallgren M. Severity of alcohol dependence in the Swedish adult population: Association with consumption and social factors. Alcohol 2013; 47: 21-25.

Aromaa A, Heliövaara M, Impivaara O, Knekt P, Maatela J, Joukamaa M et al. Terveys, toimintakyky ja hoidontarve suomessa. Mini-suomi-terveystutkimuksen perustulokset Helsinki ja Turku: Kansaneläkelaitoksen sosiaaliturvan tutkimuslaitos, Kansaneläkelaitoksen kuntoutustutkimuskeskus; 1989.

Atkinson A, Sumnall H, Begley E, Jones L. A rapid narrative review of literature on gendered alcohol marketing and its effects: Exploring the targeting and representation of women; 2019. Available at: https://www.ljmu.ac.uk/~/media/phi-reports/pdf/2019-10-ias-gendered-marketing-report.pdf (accessed 26 July, 2020)

Austin PC. A tutorial on multilevel survival analysis: Methods, models and applications. Int Stat Rev 2017; 85: 185-203.

Avendaño M, De Coulon A, Nafilyan V. Does longer compulsory schooling affect mental health? Evidence from a British reform. J Pub Econ 2020; 183: 104137.

Baron RM, Kenny DA. The moderator–mediator variable distinction in social psychological research: Conceptual, strategic, and statistical considerations. J Pers Soc Psychol 1986; 51: 1173-1182.

Barrio P, Reynolds J, García-Altés A, Gual A, Anderson P. Social costs of illegal drugs, alcohol and tobacco in the European Union: A systematic review. Drug Alcohol Rev 2017; 36: 578-588.

Baum A, Garofalo J, Yali A. Socioeconomic status and chronic stress: Does stress account for SES effects on health? Ann N Y Acad Sci 1999; 896: 131-144.

Bellis MA, Hughes K, Nicholls J, Sheron N, Gilmore I, Jones L. The alcohol harm paradox: Using a national survey to explore how alcohol may disproportionately impact health in deprived individuals. BMC Public Health 2016; 16: 111.

Berg N, Kiviruusu O, Huurre T, Lintonen T, Virtanen P, Hammarström A. Associations between unemployment and heavy episodic drinking from adolescence to midlife in Sweden and Finland. Eur J Public Health 2017; 28: 258-263.

Berg N, Kiviruusu O, Karvonen S, Kestilä L, Lintonen T, Rahkonen O, et al. A 26-year follow-up study of heavy drinking trajectories from adolescence to mid-adulthood and adult disadvantage. Alcohol Alcohol 2013; 48: 452-457.

Bjork JM, Gilman JM. The effects of acute alcohol administration on the human brain: Insights from neuroimaging. Neuropharmacology 2014; 84: 101-110.

Blas E, Kurup A. Equity, social determinants and public health programmes. Geneva: World Health Organization; 2010.

Blocker JS, Fahey DM, Tyrrell IR. Alcohol and temperance in modern history: An international encyclopedia. California, United States: ABC-CLIO; 2003.

Bloomfield K, Allamani A, Beck F, Bergmark K, Csemy L, Eisenbach-Stangl I et al. Gender, culture and alcohol problems: A multi-national study. Project final report; 2005. Available at: https://www.kettilbruun.org/projects/genacis/6.html (accessed Nov 5, 2020)

Bloomfield K, Augustin R, Kraus L. Social inequalities in alcohol use and misuse in the German general population. Zeitschrift für Gesundheitswissenschaften 2000; 8: 230-242.

Bloomfield K, Grittner U, Kramer S, Gmel G. Social inequalities in alcohol consumption and alcohol-related problems in the study countries of the EU concerted action 'Gender, culture and alcohol problems: A multi-national study'. Alcohol Alcohol Suppl 2006; 41: i26-36.

Bomford A, Sherwood RA. Acute and chronic liver disease. In: Marshall WJ, Lapsley M, Day AP & Ayling RM, editors. Clinical biochemistry: Metabolic and clinical aspects (third edition). London, United Kingdom: Churchill Livingstone; 2014, p. 250-272.

Boniface S, Shelton N. How is alcohol consumption affected if we account for under-reporting? A hypothetical scenario. Eur J Public Health 2013; 23: 1076-1081.

Borodulin K, Sääksjärvi K. FinHealth 2017 study – methods. Helsinki, Finland: Finnish Institute for Health and Welfare; 2019.

Borodulin K, Tolonen H, Jousilahti P, Jula A, Juolevi A, Koskinen S et al. Cohort profile: The National FINRISK study. Int J Epidemiol 2017; 47: 696–696i.

Borodulin K, Vartiainen E, Peltonen M, Jousilahti P, Juolevi A, Laatikainen T et al. Forty-year trends in cardiovascular risk factors in Finland. Eur J Public Health 2015; 25: 539-546.

Bosworth B. Increasing disparities in mortality by socioeconomic status. Ann Rev Public Health 2018; 39: 237-251.

Botros M, Sikaris KA. The De ritis ratio: The test of time. Clinical Biochem Rev 2013; 34: 117-130.

Bouchery EE, Harwood HJ, Sacks JJ, Simon CJ, Brewer RD. Economic costs of excessive alcohol consumption in the US, 2006. Am J Prev Med 2011; 41: 516-524.

Callinan S, Pennay A, Livingston M, Kuntsche E. Patterns of alcohol consumption in 16 cohorts of Australian young adults aged 15–24 between 2001 and 2016. Addiction 2020; 115: 1452-1458.

Carvalho AF, Heilig M, Perez A, Probst C, Rehm J. Alcohol use disorders. Lancet 2019; 394: 781-792.

Casswell S, Huckle T, Pledger M. Survey data need not underestimate alcohol consumption. Alcohol Clin Exp Res 2002; 26: 1561-1567.

Casswell S, Pledger M, Hooper R. Socioeconomic status and drinking patterns in young adults. Addiction 2003; 98: 601-610.

Cavelaars AE, Kunst AE, Mackenbach JP. Socio-economic differences in risk factors for morbidity and mortality in the European community: An international comparison. J Health Psychol 1997; 2: 353-372.

Chen Z, Roy K. Calculating concentration index with repetitive values of indicators of economic welfare. J Health Econ 2009; 28: 169-175.

Christiansen SG, Reneflot A, Stene-Larsen K, Hauge LJ. Alcohol-related mortality following the loss of a child: A register-based follow-up study from Norway. BMJ Open 2020; 10: e038826.

Ciani M, Comitini F, Mannazzu I. Fermentation. In: Jørgensen SE & Fath BD, editors. Encyclopedia of ecology. Oxford, United Kingdom: Academic Press; 2008, p. 1548-1557.

Clare P, Bradford D, Courtney RJ, Martire K, Mattick RP. The relationship between socioeconomic status and 'hardcore' smoking over time – greater accumulation of hardened smokers in low-SES than high-SES smokers. Tob Control 2014; 23: e133-e138.

Combes JB, Gerdtham UG, Jarl J. Equalisation of alcohol participation among socioeconomic groups over time: An analysis based on the total differential approach and longitudinal data from Sweden. Int J Equity Health 2011; 10: 10.

Commission on Social Determinants of Health. Closing the gap in a generation: Health equity through action on the social determinants of health. Final report of the Commission on Social Determinants of Health. Geneva, Switzerland: World Health Organization; 2008.

Conigrave KM, Davies P, Haber P, Whitfield JB. Traditional markers of excessive alcohol use. Addiction 2003; 98 Suppl 2: 31-43.

Cummings P. The relative merits of Risk ratios and Odds ratios. Arch Ped Adolesc Med 2009; 163: 438-445.

Cummins RO, Shaper AG, Walker M, Wale CJ. Smoking and drinking by middle-aged British men: Effects of social class and town of residence. BMJ 1981; 283: 1497-1502.

Cunliffe VT. The epigenetic impacts of social stress: How does social adversity become biologically embedded? Epigenomics 2016; 8: 1653-1669.

Darmon N, Drewnowski A. Does social class predict diet quality? Am J Clin Nutr 2008; 87: 1107-1117.

Davies HT, Crombie IK, Tavakoli M. When can odds ratios mislead? BMJ 1998; 316: 989-991.

Degenhardt L, Charlson F, Ferrari A, Santomauro D, Erskine H, Mantilla-Herrara A et al. The global burden of disease attributable to alcohol and drug use in 195 countries and territories, 1990-2016: A systematic analysis for the Global Burden of Disease study 2016. Lancet Psychiatry 2018; 5: 987-1012.

Departamento De Salud Pública. Estudio del costo económico y social del consumo de alcohol en Chile. Santiago, Chile: Departmento de Salud Pública, Facultad de Medicina, Pontificia Universidad Católica de Chile; 2018.

Department of Health and Social Security. Inequalities in health: Report of a research working group. London, United Kingdom: Department of Health and Social Security; 1980.

Department of Health, Education and Welfare. First special report to the US Congress on alcohol and health from the Secretary of Health, Education and Welfare. Washington, United States: Department of Health, Education and Welfare; 1971.

Devaux M, Sassi F. Social disparities in hazardous alcohol use: Self-report bias may lead to incorrect estimates. Eur J Public Health 2016; 26: 129-134.

Diderichsen F, Hallqvist J, Whitehead M. Differential vulnerability and susceptibility: How to make use of recent development in our understanding of mediation and interaction to tackle health inequalities. Int J Epidemiol 2018; 48: 268-274.

Du G, Song Z, Zhang Q. Gamma-glutamyltransferase is associated with cardiovascular and all-cause mortality: A meta-analysis of prospective cohort studies. Prev Med 2013; 57: 31-37.

Duncan GJ, Daly MC, Mcdonough P, Williams DR. Optimal indicators of socioeconomic status for health research. Am J Public Health 2002; 92: 1151-1157.

Ekholm O. Influence of the recall period on self-reported alcohol intake. Eur J Clin Nutr 2004; 58: 60-63.

Fabio A, Tu L-C, Loeber R, Cohen J. Neighborhood socioeconomic disadvantage and the shape of the age-crime curve. Am J Public Health 2011; 101 Suppl 1: S325-S332.

Faeh D, Bopp M, Swiss National Cohort Study Group. Educational inequalities in mortality and associated risk factors: German- versus French-speaking Switzerland. BMC Public Health 2010; 10: 567.

Fagerberg P, Langlet B, Oravsky A, Sandborg J, Löf M, Ioakimidis I. Ultra-processed food advertisements dominate the food advertising landscape in two Stockholm areas with low vs high socioeconomic status. Is it time for regulatory action? BMC Public Health 2019; 19: 1717.

Falkstedt D, Sorjonen K, Hemmingsson T, Deary IJ, Melin B. Psychosocial functioning and intelligence both partly explain socioeconomic inequalities in premature death. A population-based male cohort study. PLoS One 2013; 8: e82031.

Fenney K. Cash transfers and adult mortality: Evidence from pension policies. 2017. Available at: https://escholarship.org/uc/item/6f19451b#main (accessed 26 July, 2020)

Ferrie JE, Kivimäki M, Singh-Manoux A, Shortt A, Martikainen P, Head J et al. Non-response to baseline, non-response to follow-up and mortality in the Whitehall II cohort. Int J Epidemiol 2009; 38: 831-837.

Fichtenbaum R, Shahidi H. Truncation bias and the measurement of income inequality. J Bus Econ Stat 1988; 6: 335-337.

Finnish Institute for Health and Welfare. Yearbook of alcohol and drug statistics 2009, Helsinki, Finland: Finnish Institute for Health and Welfare; 2009.

Finnish Institute for Health and Welfare. Yearbook of alcohol and drug statistics 2014 Helsinki; 2014.

Finnish Institute for Health and Welfare. Yearbook of alcohol and drug statistics 2019, Helsinki, Finland: Finnish Institute for Health and Welfare; 2019.

Fry A, Littlejohns TJ, Sudlow C, Doherty N, Adamska L, Sprosen T et al. Comparison of sociodemographic and health-related characteristics of UK biobank participants with those of the general population. Am J Epidemiol 2017; 186: 1026-1034.

Fuller E, Jogantia D, Farrell M. Alcohol misuse and dependence. In: McManus S, Meltzer H, Brugha T, Bebbington P & Jenkins R, editors. Adult psychiatric morbidity in England, 2007: Results of a household survey, London, United Kingdom: NHS Information Centre for Health and Social Care; 2009.

GBD 2016 Alcohol Collaborators. Alcohol use and burden for 195 countries and territories, 1990-2016: A systematic analysis for the Global Burden of Disease study 2016. Lancet 2018; 392: 1015-1035.

Giannini EG, Testa R, Savarino V. Liver enzyme alteration: A guide for clinicians. CMAJ 2005; 172: 367-379.

Gidlow C, Johnston LH, Crone D, Ellis N, James D. A systematic review of the relationship between socio-economic position and physical activity. Health Educ J 2006; 65: 338-367.

Gil A, Polikina O, Koroleva N, McKee M, Tomkins S, Leon DA. Availability and characteristics of nonbeverage alcohols sold in 17 Russian cities in 2007. Alcohol Clin Exp Res 2009; 33: 79-85.

Gilman SE, Abrams DB, Buka SL. Socioeconomic status over the life course and stages of cigarette use: Initiation, regular use, and cessation. J Epidemiol Community Health 2003; 57: 802-808.

Gilman SE, Breslau J, Conron KJ, Koenen KC, Subramanian SV, Zaslavsky AM. Education and race-ethnicity differences in the lifetime risk of alcohol dependence. J Epidemiol Community Health 2008; 62: 224-230.

Giskes K, Turrell G, Bentley R, Kavanagh A. Individual and household-level socioeconomic position is associated with harmful alcohol consumption behaviours among adults. Aus N Z J Public Health 2011; 35: 270-277.

Cutler DM, Lleras-Muney A, Vogl T. Socioeconomic status and health: Dimensions and mechanisms. In Glied S, Smith PC, editors. Handbook of Health Economics. Oxford, United Kingdom: Oxford University Press; 2012.

Gmel G, Rehm J. Measuring alcohol consumption. Contemp Drug Probl 2004; 31: 467-540.

Gorman E, Leyland AH, Mccartney G, White IR, Katikireddi SV, Rutherford L et al. Assessing the representativeness of population-sampled health surveys through linkage to administrative data on alcohol-related outcomes. Am J Epidemiol 2014; 180: 941-948.

Grant BF, Chou SP, Saha TD, Pickering RP, Kerridge BT, Ruan WJ et al. Prevalence of 12-month alcohol use, high-risk drinking, and DSM-IV alcohol use disorder in the United States, 2001-2002 to 2012-2013: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. JAMA Psychiatry 2017; 74: 911-923.

Greenfield TK, Bond J, Kerr WC. Biomonitoring for improving alcohol consumption surveys: The new gold standard? Alcohol Res 2014; 36: 39-45.

Greenland S, Lash T, Rothman K. Concepts of interaction. In: Rothman K, Greenland S & Lash T, editors. Modern epidemiology. Philadelphia, United States: Lippincott Williams & Williams; 2008.

Grittner U, Kuntsche S, Gmel G, Bloomfield K. Alcohol consumption and social inequality at the individual and country levels--results from an international study. Eur J Public Health 2013; 23: 332-339.

Grittner U, Kuntsche S, Graham K, Bloomfield K. Social inequalities and gender differences in the experience of alcohol-related problems. Alcohol Alcohol 2012; 47: 597-605.

Halonen JI, Stenholm S, Pulakka A, Kawachi I, Aalto V, Pentti J et al. Trajectories of risky drinking around the time of statutory retirement: A longitudinal latent class analysis. Addiction 2017; 112: 1163-1170.

Harald K, Salomaa V, Jousilahti P, Koskinen S, Vartiainen E. Non-participation and mortality in different socioeconomic groups: The FINRISK population surveys in 1972-92. J Epidemiol Community Health 2007; 61: 449-454.

Harel O, Mitchell EM, Perkins NJ, Cole SR, Tchetgen Tchetgen EJ, Sun B et al. Multiple imputation for incomplete data in epidemiologic studies. Am J Epidemiol 2017; 187: 576-584.

Härkänen T, Karvanen J, Tolonen H, Lehtonen R, Djerf K, Juntunen T et al. Systematic handling of missing data in complex study designs – experiences from the Health 2000 and 2011 surveys. J Appl Stat 2016; 43: 2772-2790.

Harper S, Lynch J. Trends in socioeconomic inequalities in adult health behaviors among US States, 1990-2004. Public Health Rep 2007; 122: 177-189.

Harrell F. Regression modeling strategies: With applications to linear models, logistic and ordinal regression, and survival analysis. Switzerland: Springer; 2015.

Harrison L, Gardiner E. Do the rich really die young? Alcohol-related mortality and social class in Great Britain, 1988-94. Addiction 1999; 94: 1871-1880.

Hart A. Assembling interrelations between low socioeconomic status and acute alcohol-related harms among young adult drinkers. Contemp Drug Probl 2015; 42: 148-167.

Hasin D. Classification of alcohol use disorders. Alcohol Res Health 2003; 27: 5-17.

Hasin DS, O'Brien CP, Auriacombe M, Borges G, Bucholz K, Budney A et al. DSM-5 criteria for substance use disorders: Recommendations and rationale. Am J Psychiatry 2013; 170: 834-851.

Heckley G, Nordin M, Gerdtham U-G. The health returns of university eligibility. Working paper No. 2020:7. Lund, Sweden: Lund University; 2020.

Heistaro S. Methodology report: Health 2000 Survey. Helsinki, Finland: National Public Health Institute; 2008.

Helakorpi S, Hostila A-L, Virtanen S, Uutela A. Suomalaisen aikuisväestön terveyskäyttäytyminen ja terveys: Kevät 2011 [health behavior and health among the finnish adult population: Spring 2011. 2012. Available at: http://urn.fi/URN:ISBN:978-952-245-566-6 (accessed 16 Nov, 2020)

Helakorpi S, Mäkelä P, Uutela A. Alcohol consumption before and after a significant reduction of alcohol prices in 2004 in finland: Were the effects different across population subgroups? Alcohol Alcohol 2010; 45: 286-292.

Helakorpi S, Paavola M, Prättälä R, Uutela A. Health behavior and health of the Finnish adult population, Spring 2008. Helsinki, Finland: Finnish Institute for Health and Welfare; 2009.

Helasoja V, Lahelma E, Prattala R, Petkeviciene J, Pudule I, Tekkel M. The sociodemographic patterning of drinking and binge drinking in Estonia, Latvia, Lithuania and Finland, 1994-2002. BMC Public Health 2007; 7: 241.

Hemström O. Alcohol-related deaths contribute to socioeconomic differentials in mortality in Sweden. Eur J Public Health 2002; 12: 254-262.

Henderson A, Robinson M, McAdams R, McCartney G, Beeston C. Tracking biases: An update to the validity and reliability of alcohol retail sales data for estimating population consumption in Scotland. Alcohol Alcohol 2016; 51: 363-366.

Henderson M, Page L. Appraising the evidence: What is selection bias? Evid Based Mental Health 2007; 10: 67-68.

Herttua K, Mäkelä P, Martikainen P. Changes in alcohol-related mortality and its socioeconomic differences after a large reduction in alcohol prices: A natural experiment based on register data. Am J Epidemiol 2008; 168: 1110-1118.

Herttua K, Mäkelä P, Martikainen P. Differential trends in alcohol-related mortality: A register-based follow-up study in Finland in 1987-2003. Alcohol Alcohol 2007; 42: 456-464.

Holmes AJ, Anderson K. Convergence in national alcohol consumption patterns: New global indicators. J Wine Econ 2017; 12: 117-148.

Hosseinpoor AR, Bergen N, Kunst A, Harper S, Guthold R, Rekve D et al. Socioeconomic inequalities in risk factors for non communicable diseases in low-income and middle-income countries: Results from the World Health Survey. BMC Public Health 2012; 12: 912.

Hovda KE, Hunderi OH, Tafjord A-B, Dunlop O, Rudberg N, Jacobsen D. Methanol outbreak in Norway 2002–2004: Epidemiology, clinical features and prognostic signs. J Intern Med 2005; 258: 181-190.

Hussein M, Diez Roux AV, Mujahid MS, Hastert TA, Kershaw KN, Bertoni AG et al. Unequal exposure or unequal vulnerability? Contributions of neighborhood conditions and cardiovascular risk factors to socioeconomic inequality in incident cardiovascular disease in the Multi-Ethnic Study of Atherosclerosis. Am J Epidemiol 2017; 187: 1424-1437.

Imai K, Keele L, Yamamoto T. Identification, inference and sensitivity analysis for causal mediation effects. Statist Sci 2010; 25: 51-71.

Ingall GB. Alcohol biomarkers. Clin Lab Med 2012; 32: 391-406.

Jacobi F, Höfler M, Siegert J, Mack S, Gerschler A, Scholl L et al. Twelve-month prevalence, comorbidity and correlates of mental disorders in Germany: The mental health module of the German Health Interview and Examination Survey for Adults (DEGS1-MH). Int J Methods Psychiatr Res 2014; 23: 304-319.

Järvisalo J, Maatela J, Mäki J, Marniemi J, Reunanen A. Health-based reference values of the Mini-Finland health survey: 1. Serum gamma-glutamyltransferase, aspartate aminotransferase and alkaline phosphatase. Scand J Clin Lab Invest 1989; 49: 623-632.

Jepsen P, Vilstrup H, Andersen PK, Sørensen HT. Socioeconomic status and survival of cirrhosis patients: A Danish nationwide cohort study. BMC Gastroenterology 2009; 9: 35-35.

Jones L, Bates G, Mccoy E, Bellis MA. Relationship between alcohol-attributable disease and socioeconomic status, and the role of alcohol consumption in this relationship: A systematic review and meta-analysis. BMC Public Health 2015; 15: 400.

Jones L, Mccoy E, Bates G, Bellis M, Sumnall H. Understanding the alcohol harm paradox in order to focus the development of interventions. 2015. Available at: https://alcoholchange.org.uk/publication/understanding-the-alcohol-harm-paradox (accessed June 21, 2020)

Jorge KO, Paiva PCP, Ferreira EFE, Vale MPD, Kawachi I, Zarzar PM. Alcohol intake among adolescent students and association with social capital and socioeconomic status. Cien Saude Colet 2018; 23: 741-750.

Jousilahti P, Salomaa V, Kuulasmaa K, Niemelä M, Vartiainen E. Total and cause specific mortality among participants and non-participants of population based health surveys: A comprehensive follow up of 54 372 Finnish men and women. J Epidemiol Community Health 2005; 59: 310-315.

Kalaydjian A, Swendsen J, Chiu WT, Dierker L, Degenhardt L, Glantz M et al. Sociodemographic predictors of transitions across stages of alcohol use, disorders, and remission in the National Comorbidity Survey Replication. Compr Psychiatry 2009; 50: 299-306.

Karriker-Jaffe KJ, Zemore SE, Mulia N, Jones-Webb R, Bond J, Greenfield TK. Neighborhood disadvantage and adult alcohol outcomes: Differential risk by race and gender. J Stud Alcohol Drugs 2012; 73: 865-873.

Katikireddi SV, Whitley E, Lewsey J, Gray L, Leyland AH. Socioeconomic status as an effect modifier of alcohol consumption and harm: Analysis of linked cohort data. Lancet Public Health 2017; 2: e267-e276.

Keller M. A historical overview of alcohol and alcoholism. Cancer Res 1979; 39: 2822-2829.

Kendler K, Larsson S, Salvatore S, Sundquist J, Sundquist K. Effect of marriage on risk for onset of alcohol use disorder: A longitudinal and co-relative analysis in a Swedish national sample. Am J Psychiatry 2016; 173: 911-918.

Kendler KS, Lönn SL, Salvatore J, Sundquist J, Sundquist K. Divorce and the onset of alcohol use disorder: A Swedish population-based longitudinal cohort and co-relative study. Am J Psychiatry 2017; 174: 451-458.

Keogh RH, Park JY, White IR, Lentjes MaH, McTaggart A, Bhaniani A et al. Estimating the alcohol–breast cancer association: A comparison of diet diaries, FFQs and combined measurements. Eur J Epidemiol 2012; 27: 547-559.

Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 2005; 62: 593-602.

Kessler RC, Mcgonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. Arch Gen Psychiatry 1994; 51: 8-19.

Kessler RC, Ustun TB. The World Mental Health (WMH) survey initiative version of the World Health Organization (WHO) Composite International Diagnostic Interview (CIDI). Int J Methods Psychiatr Res 2004; 13: 93-121.

Kestilä L, Martelin T, Rahkonen O, Joutsenniemi K, Pirkola S, Poikolainen K et al. Childhood and current determinants of heavy drinking in early adulthood. Alcohol Alcohol 2008; 43: 460-469.

Keyes KM, Hatzenbuehler ML, McLaughlin KA, Link B, Olfson M, Grant BF et al. Stigma and treatment for alcohol disorders in the United States. Am J Epidemiol 2010; 172: 1364-1372.

Khang Y-H, Yun S-C, Lynch JW. Monitoring trends in socioeconomic health inequalities: It matters how you measure. BMC public health 2008; 8: 66.

Kivimäki M, Gunnell D, Lawlor DA, Davey Smith G, Pentti J, Virtanen M et al. Social inequalities in antidepressant treatment and mortality: A longitudinal register study. Psychol Med 2007; 37: 373-382.

Kivimäki M, Vähtera J, Virtanen M, Elovainio M, Pentti J, Ferrie JE. Temporary employment and risk of overall and cause-specific mortality. Am J Epidemiol 2003; 158: 663-668.

Knudsen AK, Hotopf M, Skogen JC, Øverland S, Mykletun A. The health status of nonparticipants in a population-based health study: The Hordaland Health study. Am J Epidemiol 2010; 172: 1306-1314.

Korn EL, Graubard BI, Midthune D. Time-to-event analysis of longitudinal follow-up of a survey: Choice of the time-scale. Am J Epidemiol 1997; 145: 72-80.

Koskinen S, Martelin T. Why are socioeconomic mortality differences smaller among women than among men? Soc Sci Med 1994; 38: 1385-1396.

Kringlen E, Torgersen S, Cramer V. A Norwegian psychiatric epidemiological study. Am J Psychiatry 2001; 158: 1091-1098.

Kunutsor SK, Apekey TA, Cheung BM. Gamma-glutamyltransferase and risk of hypertension: A systematic review and dose-response meta-analysis of prospective evidence. J Hypertens 2015; 33: 2373-2381.

Lachner G, Wittchen HU, Perkonigg A, Holly A, Schuster P, Wunderlich U et al. Structure, content and reliability of the Munich-Composite International Diagnostic Interview (M-CIDI) substance use sections. Eur Addict Res 1998; 4: 28-41.

Lahti RA. From findings to statistics: An assessment of Finnish medical cause-of-death information in relation to underlying-cause coding. Helsinki, Finland: University of Helsinki; 2005.

Lahti RA, Penttilä A. The validity of death certificates: Routine validation of death certification and its effects on mortality statistics. Forensic Sci Int 2001; 115: 15-32.

Lahti RA, Penttilä A. Cause-of-death query in validation of death certification by expert panel; effects on mortality statistics in Finland, 1995. Forensic Sci Int 2003; 131: 113-124.

Landberg J, Hemmingsson T, Sydén L, Ramstedt M. The contribution of alcohol use, other lifestyle factors and working conditions to socioeconomic differences in sickness absence. Eur Addict Res 2020; 26: 40-51.

Lange T, Hansen JV. Direct and indirect effects in a survival context. Epidemiology 2011; 22: 575-581.

Lantz PM, House JS, Mero RP, Williams DR. Stress, life events, and socioeconomic disparities in health: Results from the Americans' Changing Lives study. J Health Soc Behav 2005; 46: 274-288.

Latvala A, Kuja-Halkola R, D'onofrio BM, Larsson H, Lichtenstein P. Cognitive ability and risk for substance misuse in men: Genetic and environmental correlations in a longitudinal nation-wide family study. Addiction 2016; 111: 1814-1822.

Latvala A, Tuulio-Henriksson A, Perälä J, Saarni SI, Aalto-Setälä T, Aro H et al. Prevalence and correlates of alcohol and other substance use disorders in young adulthood: A population-based study. BMC Psychiatry 2009; 9: 73-73.

Lee DH, Ha MH, Christiani DC. Body weight, alcohol consumption and liver enzyme activity — a 4-year follow-up study. Int J Epidemiol 2001; 30: 766-770.

Lee S, Guo WJ, Tsang A, He YL, Huang YQ, Zhang MY et al. Associations of cohort and socio-demographic correlates with transitions from alcohol use to disorders and remission in Metropolitan China. Addiction 2009; 104: 1313-1323.

Lehtonen R, Pahkinen E. Practical methods for design and analysis of complex surveys, Second edition. Chichester, England: Wiley & Sons; 2003.

Leinsalu M, Vågerö D, Kunst AE. Estonia 1989–2000: Enormous increase in mortality differences by education. Int J Epidemiol 2003; 32: 1081-1087.

Leon DA, Saburova L, Tomkins S, Andreev E, Kiryanov N, McKee M et al. Hazardous alcohol drinking and premature mortality in Russia: A population based case-control study. Lancet 2007; 369: 2001-2009.

Lewer D, Jayatunga W, Aldridge RW, Edge C, Marmot M, Story A et al. Premature mortality attributable to socioeconomic inequality in England between 2003 and 2018: An observational study. Lancet Public Health 2020; 5: e33-e41.

Lewer D, Meier P, Beard E, Boniface S, Kaner E. Unravelling the alcohol harm paradox: A population-based study of social gradients across very heavy drinking thresholds. BMC Public Health 2016; 16: 599.

Leyland AH, Dundas R, McLoone P, Boddy FA. Cause-specific inequalities in mortality in Scotland: Two decades of change. A population-based study. BMC Public Health 2007; 7: 172.

Litten RZ, Bradley AM, Moss HB. Alcohol biomarkers in applied settings: Recent advances and future research opportunities. Alcohol Clin Exp Res 2010; 34: 955-967.

Liu C-C, Lu C-L, Notobroto HB, Tsai C-C, Wen P-H, Li C-Y. Individual and neighborhood socioeconomic status in the prediction of liver transplantation among patients with liver disease: A population-based cohort study in Taiwan. Medicine 2019; 98: e14849.

Liu Y, Lintonen T, Tynjälä J, Villberg J, Välimaa R, Ojala K et al. Socioeconomic differences in the use of alcohol and drunkenness in adolescents: Trends in the Health Behaviour in School-aged Children study in Finland 1990–2014. Scand J Public Health 2016; 46: 102-111.

Livingston M, Callinan S. Underreporting in alcohol surveys: Whose drinking is underestimated? J Stud Alcohol Drugs 2015; 76: 158-164.

Lorant V, Demarest S, Miermans P-J, Van Oyen H. Survey error in measuring socio-economic risk factors of health status: A comparison of a survey and a census. Int J Epidemiol 2007; 36: 1292-1299.

Loring B. Alcohol and inequities: Guidance for addressing inequities in alcohol-related harm. Geneva, Switzerland: World Health Organization; 2014.

Loucks EB, Buka SL, Rogers ML, Liu T, Kawachi I, Kubzansky LD et al. Education and coronary heart disease risk associations may be affected by early-life common prior causes: A propensity matching analysis. Ann Epidemiol 2012; 22: 221-232.

Lui CK, Kerr WC, Mulia N, Ye Y. Educational differences in alcohol consumption and heavy drinking: An age-period-cohort perspective. Drug Alcohol Depend 2018; 186: 36-43.

Lundqvist A, Mäki-Opas T. Health 2011 survey - methods. Helsinki, Finland: National Institute for Health and Welfare; 2016.

Lunetta P, Lounamaa A, Sihvonen S. Surveillance of injury-related deaths: Medicolegal autopsy rates and trends in Finland. Inj Prev 2007; 13: 282-284.

Mackenbach JP, Kulhanova I, Bopp M, Borrell C, Deboosere P, Kovacs K et al. Inequalities in alcohol-related mortality in 17 European countries: A retrospective analysis of mortality registers. PLoS Med 2015; 12: e1001909.

Mackenbach JP, Kunst AE. Measuring the magnitude of socio-economic inequalities in health: An overview of available measures illustrated with two examples from Europe. Soc Sci Med 1997; 44: 757-771.

Mackenbach JP, Rubio Valverde J, Bopp M, Brønnum-Hansen H, Costa G, Deboosere P et al. Progress against inequalities in mortality: Register-based study of 15 European countries between 1990 and 2015. Eur J Epidemiol 2019; 34: 1131-1142.

Mackenbach JP, Stirbu I, Roskam A-JR, Schaap MM, Menvielle G, Leinsalu M et al. Socioeconomic inequalities in health in 22 European countries. N Engl J Med 2008; 358: 2468-2481.

MacKinnon DP, Krull JL, Lockwood CM. Equivalence of the mediation, confounding and suppression effect. Prev Sci 2000; 1: 173-181.

Maclennan B, Kypri K, Langley J, Room R. Non-response bias in a community survey of drinking, alcohol-related experiences and public opinion on alcohol policy. Drug Alcohol Depend 2012; 126: 189-194.

Maggs JL, Schulenberg JE. Trajectories of alcohol use during the transition to adulthood. Alcohol Res Health 2004; 28: 195-201.

Mäkelä P. Alcohol-related mortality as a function of socio-economic status. Addiction 1999; 94: 867-886.

Mäkelä P, Herttua K, Martikainen P. The socioeconomic differences in alcohol-related harm and the effects of alcohol prices on them: A summary of evidence from Finland. Alcohol Alcohol 2015; 50: 661-669.

Mäkelä P, Huhtanen P. The effect of survey sampling frame on coverage: The level of and changes in alcohol-related mortality in Finland as a test case. Addiction 2010; 105: 1935-1941.

Mäkelä P, Keskimäki I, Koskinen S. What underlies the high alcohol related mortality of the disadvantaged: High morbidity or poor survival? J Epidemiol Community Health 2003; 57: 981-986.

Mäkelä P, Paljärvi T. Do consequences of a given pattern of drinking vary by socioeconomic status? A mortality and hospitalisation follow-up for alcohol-related causes of the Finnish Drinking Habits surveys. J Epidemiol Community Health 2008; 62: 728-733.

Manor O, Matthews S, Power C. Comparing measures of health inequality. Soc Sci Med 1997; 45: 761-771.

Marmot M. Fair society, healthy lives: The Marmot review: Strategic review of health inequalities in England post-2010. London, United Kingdom: Department of Health, England; 2010.

Martikainen P. Unemployment and mortality among Finnish men, 1981-5. BMJ 1990; 301: 407-411.
Martikainen P, Laaksonen M, Piha K, Lallukka T. Does survey non-response bias the association between occupational social class and health? Scand J Public Health 2007; 35: 212-215.
Martikainen P, Mäkelä P, Koskinen S, Valkonen T. Income differences in mortality: A register-based follow-up study of three million men and women. Int J Epidemiol 2001; 30: 1397-1405.
Martins JG, Guimarães MO, Jorge KO, Silva CJDP, Ferreira RC, Pordeus IA et al. Binge drinking, alcohol outlet density and associated factors: A multilevel analysis among adolescents in Belo Horizonte, Minas Gerais state, Brazil. Cadernos de Saúde Pública 2020; 36: e00052119.
Matsuyama Y, Aida J, Tsuboya T, Hikichi H, Kondo K, Kawachi I et al. Are lowered socioeconomic circumstances causally related to tooth loss? A natural experiment involving the 2011 Great East Japan earthquake. Am J Epidemiol 2017; 186: 54-62.
Matthay EC, Glymour MM. A graphical catalog of threats to validity: Linking social science with epidemiology. Epidemiology 2020; 31: 376-384.
McCartney G, Popham F, McMaster R, Cumbers A. Defining health and health inequalities. Public Health 2019; 172: 22-30.
McCutcheon A. Sampling bias. In: Lavrakas P, editor. Encyclopedia of survey research methods. Thousand Oaks, California: SAGE Publications; 2008.
McGovern PE, Zhang J, Tang J, Zhang Z, Hall GR, Moreau RA et al. Fermented beverages of pre- and proto-historic China. Proc Natl Acad Sci USA 2004; 101: 17593-17598.
McLaren L. Socioeconomic status and obesity. Epidemiol Rev 2007; 29: 29-48.
McMinn MA, Gray L, Harkanen T, Tolonen H, Pitkanen J, Molaodi OR et al. Alcohol-related outcomes and all-cause mortality in the Health 2000 Survey by participation status and compared with the Finnish population. Epidemiology 2020; 31: 534-541.
Mendoza-Sassi RA, Béria JU. Prevalence of alcohol use disorders and associated factors: A population-based study using AUDIT in Southern Brazil. Addiction 2003; 98: 799-804.
Midanik LT, Clark WB. The demographic distribution of us drinking patterns in 1990: Description and trends from 1984. Am J Public Health 1994; 84: 1218-1222.
Mikkelsen L, Phillips DE, Abouzahr C, Setel PW, De Savigny D, Lozano R et al. A global assessment of civil registration and vital statistics systems: Monitoring data quality and progress. Lancet 2015; 386: 1395-1406.
Ministerio de Salud. Encuesta Nacional de Salud ENS Chile 2009-2010. Santiago, Chile: Ministerio de Salud; 2014.
Ministerio de Salud. Encuestas poblacionales - cuestionarios. 2020. Available at: http://epi.minsal.cl/cuestionarios/ (accessed July 2, 2020)
Ministry of Social Affairs and Health. Law 459. Law on determining the cause of death; 1973.
Ministry of Social Affairs and Health. National action plan to reduce health inequalities 2008-2011. Helsinki, Finland: Ministry of Social Affairs and Health; 2008.
Montalto NJ, Bean P. Use of contemporary biomarkers in the detection of chronic alcohol use. Med Sci Monit 2003; 9: RA285-290.
Mullahy J, Sindelar J. Life-cycle effects of alcoholism on education, earnings, and occupation. Inquiry 1989; 26: 272-282.
Nandi A, Glymour MM, Kawachi I, Vanderweele TJ. Using marginal structural models to estimate the direct effect of adverse childhood social conditions on onset of heart disease, diabetes, and stroke. Epidemiology 2012; 23: 223-232.

Nayak MB, Patterson D, Wilsnack SC, Karriker-Jaffe KJ, Greenfield TK. Alcohol's secondhand harms in the United States: New data on prevalence and risk factors. J Stud Alcohol Drugs 2019; 80: 273-281.

Needham BL, Smith JA, Zhao W, Wang X, Mukherjee B, Kardia SLR et al. Life course socioeconomic status and DNA methylation in genes related to stress reactivity and inflammation: The Multi-Ethnic Study of Atherosclerosis. Epigenetics 2015; 10: 958-969.

Niemelä O. Biomarker-based approaches for assessing alcohol use disorders. Int J Environ Res Public Health 2016; 13: 166.

Niemelä O, Alatalo P. Biomarkers of alcohol consumption and related liver disease. Scand J Clin Lab Invest 2010; 70: 305-312.

Niemelä O, Niemelä M, Bloigu R, Aalto M, Laatikainen T. Where should the safe limits of alcohol consumption stand in light of liver enzyme abnormalities in alcohol consumers? PLoS One 2017; 12: e0188574.

Nordahl H, Diderichsen F, Hvidtfeldt UA, Lange T, Andersen PK, Osler M et al. Joint effect of alcohol consumption and educational level on alcohol-related medical events: A Danish register-based cohort study. Epidemiology 2017; 28: 872-879.

Norström T, Romelsjö A. Social class, drinking and alcohol-related mortality. J Subst Abuse 1998; 10: 385-395.

O'Donnell O, Van Doorslaer E, Wagstaff A, Lindelow M. Analyzing health equity using household survey data: A guide to techniques and their implementation. Washington, DC: International Bank for Reconstruction and Development / The World Bank; 2008.

Obradors-Rial N, Ariza C, Rajmil L, Muntaner C. Socioeconomic position and occupational social class and their association with risky alcohol consumption among adolescents. Int J Public Health 2018; 63: 457-467.

Oldham M, Callinan S, Whitaker V, Fairbrother H, Curtis P, Meier P et al. The decline in youth drinking in England—is everyone drinking less? A quantile regression analysis. Addiction 2020; 115: 230-238.

Osler M, Kriegbaum M, Christensen U, Holstein B, Nybo Andersen A-M. Rapid report on methodology: Does loss to follow-up in a cohort study bias associations between early life factors and lifestyle-related health outcomes? Ann Epidemiol 2008; 18: 422-424.

Osna NA, Kharbanda KK. Multi-organ alcohol-related damage: Mechanisms and treatment. Biomolecules 2016; 6: 20.

Paasma R, Hovda KE, Tikkerberi A, Jacobsen D. Methanol mass poisoning in Estonia: Outbreak in 154 patients. Clin Toxicol 2007; 45: 152-157.

Pabst A, Van Der Auwera S, Piontek D, Baumeister SE, Kraus L. Decomposing social inequalities in alcohol consumption in Germany 1995–2015: An age–period–cohort analysis. Addiction 2019; 114: 1359-1368.

Pagh Møller S, Pisinger VSC, Illemann Christensen A, Schurmann Tolstrup J. Socioeconomic position and alcohol related harm in Danish teenagers. Rev Épidemiol Sante Publique 2018; 66: S256.

Paljärvi T, Martikainen P, Pensola T, Leinonen T, Herttua K, Mäkelä P. Life course trajectories of labour market participation among young adults who experienced severe alcohol-related health outcomes: A retrospective cohort study. PLoS One 2015; 10: e0126215.

Paljärvi T, Suominen S, Car J, Koskenvuo M. Socioeconomic disadvantage and indicators of risky alcohol-drinking patterns. Alcohol Alcohol 2012; 48: 207-214.

Pape H, Rossow I, Andreas JB, Norström T. Social class and alcohol use by youth: Different drinking behaviors, different associations? J Stud Alcohol Drugs 2018; 79: 132-136.

Pape H, Rossow I, Brunborg GS. Adolescents drink less: How, who and why? A review of the recent research literature. Drug Alcohol Rev 2018; 37: S98-S114.

Parna K, Rahu K, Helakorpi S, Tekkel M. Alcohol consumption in Estonia and Finland: Finbalt survey 1994-2006. BMC Public Health 2010; 10: 261.

Pechey R, Monsivais P. Socioeconomic inequalities in the healthiness of food choices: Exploring the contributions of food expenditures. Prev Med 2016; 88: 203-209.

Pinto-Meza A, Moneta MV, Alonso J, Angermeyer MC, Bruffaerts R, Caldas De Almeida JM et al. Social inequalities in mental health: Results from the EU contribution to the World Mental Health surveys initiative. Soc Psychiatry Psychiatr Epidemiol 2013; 48: 173-181.

Pirkola SP, Poikolainen K, Lonnqvist JK. Currently active and remitted alcohol dependence in a nationwide adult general population--results from the Finnish Health 2000 study. Alcohol Alcohol 2006; 41: 315-320.

Popova S, Lange S, Probst C, Gmel G, Rehm J. Estimation of national, regional, and global prevalence of alcohol use during pregnancy and fetal alcohol syndrome: A systematic review and meta-analysis. Lancet Global Health 2017; 5: e290-e299.

Pridemore WA, Tomkins S, Eckhardt K, Kiryanov N, Saburova L. A case-control analysis of socio-economic and marital status differentials in alcohol- and non-alcohol-related mortality among working-age Russian males. Eur J Public Health 2010; 20: 569-575.

Probst C, Parry CDH, Wittchen H-U, Rehm J. The socioeconomic profile of alcohol-attributable mortality in South Africa: A modelling study. BMC Medicine 2018; 16: 97.

Probst C, Roerecke M, Behrendt S, Rehm J. Socioeconomic differences in alcohol-attributable mortality compared with all-cause mortality: A systematic review and meta-analysis. Int J Epidemiol 2014; 43: 1314-1327.

Probst C, Roerecke M, Behrendt S, Rehm J. Gender differences in socioeconomic inequality of alcohol-attributable mortality: A systematic review and meta-analysis. Drug Alcohol Rev 2015; 34: 267-277.

Rahu K, Pärna K, Palo E, Rahu M. Contrasts in alcohol-related mortality in Estonia: Education and ethnicity. Alcohol Alcohol 2009; 44: 517-522.

Raitasalo K, Kraus L, Bye EK, Karlsson P, Tigerstedt C, Törrönen J et al. Similar countries, similar factors? Studying the decline of heavy episodic drinking in adolescents in Finland, Norway and Sweden. Addiction 2020 (in press), https://doi.org/10.1111/add.15089.

Ramsay JO, Heckman N, Silverman BW. Spline smoothing with model-based penalties. Behav Res Methods Instrum Comput 1997; 29: 99-106.

Ranaweera S, Amarasinghe H, Chandraratne N, Thavorncharoensap M, Ranasinghe T, Karunaratna S et al. Economic costs of alcohol use in Sri Lanka. PLoS One 2018; 13: e0198640.

Rao R, Topiwala A. Alcohol use disorders and the brain. Addiction 2020; 115: 1580-1589.

Ratna A, Mandrekar P. Alcohol and cancer: Mechanisms and therapies. Biomolecules 2017; 7: 61.

Regidor E. Measures of health inequalities: Part 1. J Epidemiol Community Health 2004; 58: 858-861.

Regidor E. Measures of health inequalities: Part 2. J Epidemiol Community Health 2004; 58: 900-903.

Rehm J. The risks associated with alcohol use and alcoholism. Alcohol Res Health 2011; 34: 135-143.

Rehm J, Gmel GE, Sr., Gmel G, Hasan OSM, Imtiaz S, Popova S et al. The relationship between different dimensions of alcohol use and the burden of disease-an update. Addiction 2017; 112: 968-1001.

Rehm J, Mathers C, Popova S, Thavorncharoensap M, Teerawattananon Y, Patra J. Global burden of disease and injury and economic cost attributable to alcohol use and alcohol-use disorders. Lancet 2009; 373: 2223-2233.

Rehm J, Scafato E. Indicators of alcohol consumption and attributable harm for monitoring and surveillance in European Union countries. Addiction 2011; 106: 4-10.

Rehm J, Shield KD. Global burden of disease and the impact of mental and addictive disorders. Curr Psychiatry Rep 2019; 21: 10.

Reinikainen J, Tolonen H, Borodulin K, Harkanen T, Jousilahti P, Karvanen J et al. Participation rates by educational levels have diverged during 25 years in Finnish health examination surveys. Eur J Public Health 2018; 28: 237-243.

Robins JM, Hernán MÁ, Brumback B. Marginal structural models and causal inference in epidemiology. Epidemiology 2000; 11: 550-560.

Robinson M, Thorpe R, Beeston C, McCartney G. A review of the validity and reliability of alcohol retail sales data for monitoring population levels of alcohol consumption: A Scottish perspective. Alcohol Alcohol 2013; 48: 231-240.

Rod NH, Lange T, Andersen I, Marott JL, Diderichsen F. Additive interaction in survival analysis: Use of the additive hazards model. Epidemiology 2012; 23: 733-737.

Romelsjö A, Lundberg M. The changes in the social class distribution of moderate and high alcohol consumption and of alcohol-related disabilities over time in Stockholm county and in Sweden. Addiction 1996; 91: 1307-1324.

Room R, Callinan S, Greenfield TK, Rekve D, Waleewong O, Stanesby O et al. The social location of harm from others' drinking in 10 societies. Addiction 2019; 114: 425-433.

Rosoff DB, Clarke T-K, Adams MJ, Mcintosh AM, Davey Smith G, Jung J et al. Educational attainment impacts drinking behaviors and risk for alcohol dependence: Results from a two-sample mendelian randomization study with ~780,000 participants. Mol Psychiatry 2019; in press https://doi.org/10.1038/s41380-019-0535-9.

Sadler S, Angus C, Gavens L, Gillespie D, Holmes J, Hamilton J et al. Understanding the alcohol harm paradox: An analysis of sex- and condition-specific hospital admissions by socio-economic group for alcohol-associated conditions in England. Addiction 2017; 112: 808-817.

Sassi F. Tackling harmful alcohol use. Paris, France: OECD Publishing; 2015.

Scheike TH, Martinussen T. Dynamic regression models for survival data. New York: Springer; 2006.

Schmidt L, Mäkelä P, Rehm J, Room R. Alcohol: Equity and social determinants. In: Blas E & Kurup A, editors. Equity, social determinants and public health programmes. Geneva, Switzerland: World Health Organization; 2010.

Schou L, Moan IS. Alcohol use–sickness absence association and the moderating role of gender and socioeconomic status: A literature review. Drug Alcohol Rev 2016; 35: 158-169.

Shield K, Manthey J, Rylett M, Probst C, Wettlaufer A, Parry CDH et al. National, regional, and global burdens of disease from 2000 to 2016 attributable to alcohol use: A comparative risk assessment study. Lancet Public Health 2020; 5: e51-e61.

Shield KD, Parry C, Rehm J. Chronic diseases and conditions related to alcohol use. Alcohol Res Curr Rev 2013; 35: 155-173.

Shkolnikov VM, Leon DA, Adamets S, Eugeniy A, Deev A. Educational level and adult mortality in Russia: An analysis of routine data 1979 to 1994. Soc Sci Med 1998; 47: 357-369.

Silveira CM, Viana MC, Siu ER, De Andrade AG, Anthony JC, Andrade LH. Sociodemographic correlates of transitions from alcohol use to disorders and remission in the São Paulo Megacity Mental Health survey, Brazil. Alcohol Alcohol 2011; 46: 324-332.

Smyth A, Teo KK, Rangarajan S, O'donnell M, Zhang X, Rana P et al. Alcohol consumption and cardiovascular disease, cancer, injury, admission to hospital, and mortality: A prospective cohort study. Lancet 2015; 386: 1945-1954.

Sobell LC, Sobell MB. Timeline follow-back. In: Litten RZ & Allen JP, editors. Measuring alcohol consumption: Psychosocial and biochemical methods. Totowa, United States: Humana Press; 1992, p. 41-72.

Solomons HD. Carbohydrate deficient transferrin and alcoholism. Germs 2012; 2: 75-78.

Sordo L, Barrio G, Bravo MJ, Villalbí JR, Espelt A, et al. Estimating average alcohol consumption in the population using multiple sources: The case of Spain. Popul Health Metr 2016; 14: 21.

Statistics Finland. Statistics Finland PX-web databases. 2017. Available at: https://pxnet2.stat.fi/PXWeb/pxweb/en/StatFin/ (accessed Nov 16, 2020).

Statistics Finland. Quality description: Causes of death 2018. 2018. Available at: http://www.stat.fi/til/ksyyt/2018/ksyyt_2018_2019-12-16_laa_001_en.html (accessed May 1, 2020)

Statistics Finland. Population structure. 2020. Available at: https://www.stat.fi/meta/til/vaerak_en.html (accessed July 2, 2020)

Steele L, Dewa C, Lee K. Socioeconomic status and self-reported barriers to mental health service use. Can J Psychiatry 2007; 52: 201-206.

Stockwell T, Donath S, Cooper-Stanbury M, Chikritzhs T, Catalano P, Mateo C. Under-reporting of alcohol consumption in household surveys: A comparison of quantity–frequency, graduated–frequency and recent recall. Addiction 2004; 99: 1024-1033.

Stringhini S, Carmeli C, Jokela M, Avendano M, Muennig P, Guida F et al. Socioeconomic status and the 25 x 25 risk factors as determinants of premature mortality: A multicohort study and meta-analysis of 1.7 million men and women. Lancet 2017; 389: 1229-1237.

Stringhini S, Polidoro S, Sacerdote C, Kelly RS, Van Veldhoven K, Agnoli C et al. Life-course socioeconomic status and DNA methylation of genes regulating inflammation. Int J Epidemiol 2015; 44: 1320-1330.

Stringhini S, Zaninotto P, Kumari M, Kivimäki M, Lassale C, Batty GD. Socio-economic trajectories and cardiovascular disease mortality in older people: The English Longitudinal Study of Ageing. Int J Epidemiol 2017; 47: 36-46.

Sydén L, Sidorchuk A, Mäkelä P, Landberg J. The contribution of alcohol use and other behavioural, material and social factors to socio-economic differences in alcohol-related disorders in a Swedish cohort. Addiction 2017; 112: 1920-1930.

Takayanagi Y, Spira AP, Roth KB, Gallo JJ, Eaton WW, Mojtabai R. Accuracy of reports of lifetime mental and physical disorders: Results from the Baltimore Epidemiological Catchment Area study. JAMA Psychiatry 2014; 71: 273-280.

Talala K, Huurre T, Aro H, Martelin T, Prättälä R. Socio-demographic differences in self-reported psychological distress among 25- to 64-year-old Finns. Soc Ind Res 2008; 86: 323-335.

Tarkiainen L, Martikainen P, Laaksonen M. The contribution of education, social class and economic activity to the income-mortality association in alcohol-related and other mortality in Finland in 1988-2012. Addiction 2016; 111: 456-464.

Tarkiainen L, Rehnberg J, Martikainen P, Fritzell J. Income trajectories prior to alcohol-attributable death in Finland and Sweden. Addiction 2019; 114: 807-814.

Tavakoli HR, Hull M, Michael Okasinski L. Review of current clinical biomarkers for the detection of alcohol dependence. Innov Clin Neurosci 2011; 8: 26-33.

Teesson M, Hall W, Slade T, Mills K, Grove R, Mewton L et al. Prevalence and correlates of DSM-iv alcohol abuse and dependence in Australia: Findings of the 2007 National Survey of Mental Health and Wellbeing. Addiction 2010; 105: 2085-2094.

Thavorncharoensap M, Teerawattananon Y, Yothasamut J, Lertpitakpong C, Chaikledkaew U. The economic impact of alcohol consumption: A systematic review. Subst Abuse Treat Prev Policy 2009; 4: 20.

Therneau TM, Atkinson E. Concordance. 2019. Available at: https://cran.r-project.org/web/packages/survival/vignettes/concordance.pdf (accessed Nov 16, 2020)

Therneau TM, Grambsch PM. Functional form. Modeling survival data: Extending the cox model. New York, United States: Springer New York; 2000, p. 87-126.

Thørrisen MM, Bonsaksen T, Hashemi N, Kjeken I, Van Mechelen W, Aas RW. Association between alcohol consumption and impaired work performance (presenteeism): A systematic review. BMJ Open 2019; 9: e029184.

Tjepkema M, Wilkins R, Long A. Cause-specific mortality by income adequacy in Canada: A 16-year follow-up study. Health Rep 2013; 24: 14-22.

Tolonen H, Helakorpi S, Talala K, Helasoja V, Martelin T, Prättälä R. 25-year trends and socio-demographic differences in response rates: Finnish Adult Health Behaviour survey. Eur J Epidemiol 2006; 21: 409-415.

Tolonen H, Honkala M, Reinikainen J, Härkänen T, Mäkelä P. Adjusting for non-response in the Finnish Drinking Habits survey. Scand J Public Health 2019; 47: 469-473.

Torruellas C, French SW, Medici V. Diagnosis of alcoholic liver disease. World J Gastroenterol 2014; 20: 11684-11699.

Valkonen T. Problems in the measurement and international comparisons of socio-economic differences in mortality. Soc Sci Med 1993; 36: 409-418.

Van Beek JHDA, De Moor MHM, Geels LM, Sinke MRT, De Geus EJC, Lubke GH et al. The association of alcohol intake with γ-glutamyl transferase (GGT) levels: Evidence for correlated genetic effects. Drug Alcohol Depend 2014; 134: 99-105.

Van Buuren S. Flexible imputation of missing data. Florida, United States: Chapman & Hall/CRC; 2018.

Van Buuren S, Groothuis-Oudshoorn K. Mice: Multivariate imputation by chained equations in R. J Stat Soft 2011; 45: 1-67.

Van Kerm P. 'Sgini - generalized gini and concentration coefficients (with factor decomposition) in Stata', v1.1 (revised february 2010). Differdange, Luxemburg: CEPS/INSTEAD; 2009.

Van Loon AJM, Tijhuis M, Picavet HSJ, Surtees PG, Ormel J. Survey non-response in the Netherlands: Effects on prevalence estimates and associations. Ann Epidemiol 2003; 13: 105-110.

Van Oers JA, Bongers IM, Van De Goor LA, Garretsen HF. Alcohol consumption, alcohol-related problems, problem drinking, and socioeconomic status. Alcohol Alcohol 1999; 34: 78-88.

Vandenbroucke JP, Von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ et al. Strengthening the reporting of observational studies in epidemiology (STROBE): Explanation and elaboration. PLoS Med 2007; 4: e297.

VanderWeele TJ. A three-way decomposition of a total effect into direct, indirect, and interactive effects. Epidemiology 2013; 24: 224-232.

VanderWeele TJ. Mediation analysis: A practitioner's guide. Ann Rev Public Health 2016; 37: 17-32.
VanderWeele TJ, Knol MJ. A tutorial on interaction. Epidemiol Methods; 2014, p. 33-72.
VanderWeele TJ, Vansteelandt S. Mediation analysis with multiple mediators. Epidemiologic methods 2014; 2: 95-115.
Vonghia L, Leggio L, Ferrulli A, Bertini M, Gasbarrini G, Addolorato G. Acute alcohol intoxication. Eur J Intern Med 2008; 19: 561-567.
Voss M, Nylen L, Floderus B, Diderichsen F, Terry PD. Unemployment and early cause-specific mortality: A study based on the Swedish twin registry. Am J Public Health 2004; 94: 2155-2161.
Vroon D, Israili Z. Aminotransferases. In: Walker HK, Hall WD & Hurst JW, editors. Clinical methods: The history, physical, and laboratory examinations 3rd edition. Boston, United States: Butterworths; 1990.
Wagstaff A. The concentration index of a binary outcome revisited. Health Econ 2011; 20: 1155-1160.
Wagstaff A, Paci P, Van Doorslaer E. On the measurement of inequalities in health. Soc Sci Med 1991; 33: 545-557.
Wannamethee SG, Shaper AG. Cigarette smoking and serum liver enzymes: The role of alcohol and inflammation. Ann Clin Biochem 2010; 47: 321-326.
Whiteford HA, Degenhardt L, Rehm J, Baxter AJ, Ferrari AJ, Erskine HE et al. Global burden of disease attributable to mental and substance use disorders: Findings from the Global Burden of Disease study 2010. Lancet 2013; 382: 1575-1586.
Whitehead M, Dahlgren G. Concepts and principles for tackling social inequities in health: Levelling up part 1. Copenhagen, Denmark: WHO Regional Office for Europe; 2006.
Whitfield JB. Gamma glutamyl transferase. Crit Rev Clin Lab Sci 2001; 38: 263-355.
Wittchen HU, Lachner G, Wunderlich U, Pfister H. Test-retest reliability of the computerized DSM-IV version of the Munich-Composite International Diagnostic Interview (M-CIDI). Soc Psychiatry Psychiatr Epidemiol 1998; 33: 568-578.
Wood S, Bellis M. Socio-economic inequalities in alcohol consumption and harm: Evidence for effective interventions and policy across EU countries, Brussels: European Commission; 2017.
World Health Organization. Physical status: The use and interpretation of anthropometry. Report of a WHO expert committee. World Health Organ Tech Rep Ser 1995; 854: 1-452.
World Health Organization. Information note: Methanol poisoning outbreaks. 2014. Available at: https://www.who.int/environmental_health_emergencies/poisoning/methanol_information.pdf?ua=1 (accessed July 4, 2020)
World Health Organization. Global status report on alcohol and health 2018. Geneva, Switzerland: WHO; 2018.
World Health Organization. International statistical classification of diseases and related health problems 10th revision. 2019. Available at: https://icd.who.int/browse10/2019/en (accessed July 3, 2020)
Wray TB, Merrill JE, Monti PM. Using ecological momentary assessment (EMA) to assess situation-level predictors of alcohol use and alcohol-related consequences. Alcohol Res Curr Rev 2014; 36: 19-27.
Zagozdzon P, Zaborski L, Ejsmont J. Survival and cause-specific mortality among unemployed individuals in Poland during economic transition. J Public Health 2008; 31: 138-146.
Zhang Q, Wang Y. Using concentration index to study changes in socio-economic inequality of overweight among US adolescents between 1971 and 2002. Int J Epidemiol 2007; 36: 916-925.
Zhang Z, Reinikainen J, Adeleke KA, Pieterse ME, Groothuis-Oudshoorn CGM. Time-varying covariates and coefficients in Cox regression models. Ann Transl Med 2018; 6: 121.

Zhao J, Stockwell T, Macdonald S. Non-response bias in alcohol and drug population surveys. Drug Alcohol Rev 2009; 28: 648-657.

Zhou T, Sun D, Li X, Ma H, Heianza Y, Qi L. Educational attainment and drinking behaviors: Mendelian randomization study in UK Biobank. Mol Psychiatry 2019, in press https://doi.org/10.1038/s41380-019-0596-9.

ISBN 978-951-51-6919-8 (PRINT)
ISBN 978-951-51-6920-4 (ONLINE)
ISSN 2342-3161 (PRINT)
ISSN 2342-317X (ONLINE)
http://ethesis.helsinki.fi

HELSINKI 2021